Evolution of Ionic Channels of Biological Membranes

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This paper presents a view of the evolution and phylogenetic distribution of ionic channels of biological membranes. The view is based on the assumptions that ionic channels (1) appeared very early in the history of life, (2) have evolved from a common ancestor, and (3) have been subjected to evolutionary pressure to reach precision and high speed of signaling. We propose that Ca\(^{2+}\) was the intracellular messenger and modulator of the most primitive biological systems, which implies that the first channel to appear may have been a calcium channel. Then, very soon the entire group of potassium channels evolved from the calcium channel to improve the shape of signals and to restore initial conditions. Sodium channels probably appeared relatively late, diversifying from calcium channels in the early metazoan groups. Mainly because Na\(^{+}\) ions do not interfere with cellular metabolism (thus allowing the inward current—and, consequently, the speed of conduction—to be greatly increased), sodium channels probably proved advantageous in the generation of the action potential, and selection replaced calcium channels with sodium channels in this function. Finally, with the acquisition of multicellularity, channels responsible for synaptic transmission appeared. The case of the acetylcholine receptor channel is briefly discussed.

Introduction

Electrophysiological and biophysical methods applied to various preparations from different phyla have shown the presence of several different ionic channels in cell membranes. Most conspicuous are the voltage-gated sodium (Na) channel, the group of potassium channels—delayed rectifier (K\(_{\text{DR}}\)), inward rectifier (IK), and Ca-activated (K(\(\text{Ca}\))) potassium channels—the calcium (Ca) channel, and the acetylcholine receptor (AChR) channel of the muscle endplate.

Although differences exist among the various types of channels with respect to conductance, selectivity sequence, sensitivity to ligands, and blockers, similarities are also present. Primarily, they pertain to (1) the overall architecture of the channel (all channels are membrane proteins contacting intracellular and extracellular solutions through an internal pore showing a restriction of atomic dimension that forms the selectivity filter, (2) the all-or-none kinetics (channels show only two functional states—the closed state with zero conductance and the open state with full conductance), and (3) the properties, shared by all ionic channels, of gating and selectivity.

Another result of this comparative inspection is that evolutionarily primitive organisms show fewer types of channels than do more advanced ones. For instance,
sodium-dependent action potentials are not known in protozoa, which is indicative of the lack of Na channels in this group. Protozoa, however, show Ca channels and several K channels. Similar considerations apply to the AChR channel. On the basis of these observations we present both a view on the evolution of ionic channels that has the limited objective of providing a framework for thinking and a working hypothesis for formulating new questions.

As a guideline for the discussion that follows, we present a simplified phylogenetic tree of the major animal groups (fig. 1A; based on Minkoff 1983), as well as a phylogenetic tree of ionic channels (fig. 1B), showing their hypothetical evolutionary relationship and their distribution at low taxonomic levels. The topic of channel evolution has been briefly discussed from an excellent perspective by Hille (1984).

**Discussion**

**General**

We do not know when life began on earth or how the most primitive living structures were organized. We only know that ~3,500 Mya prokaryotes, the most ancient organisms, appeared. Although very simple in structure (they lacked nuclear membrane and mitotic apparatus, as well as intracellular organelles), they probably had an enveloping lipid membrane, whose architecture must have been accordingly simple. Membranes would probably have been beneficial to the earliest cells, since they would permit the protocell to retain vital macromolecules. However, a simple diffusion barrier that was impermeable to small molecules would not have been useful, since it would have prevented both access to needed substances and elimination of waste products. The evolution of size-selective membrane pores that retained macromolecules but passed small molecules would have partly solved the problem, but more-selective exchange pathways and transport mechanisms for both ions and nutrients would probably have been selectively advantageous.

These features were probably present in primitive eukaryotes, which appeared ~1,500 Mya, when the hydrosphere became aerobic. With the availability of oxygen, these primitive unicellular organisms could have developed mechanisms of energy production, an event that gave them great freedom: energy-fueled transport mechanisms that moved metabolites bidirectionally were now possible, regardless of their electrochemical gradient. Eukaryotes probably refined also the structure of the membrane by making it less permeable. This overall organization of the cell might have worked well enough to guarantee both survival of the organisms and the accomplishment of their primary functions, such as nutrition and osmoregulation.

Another requirement concerned communication from the outside world to the interior of the cell. This called for a suitable messenger that, from the outside, would, on certain stimuli, enter the cell and evoke specific biological responses.

**Ca as Intracellular Messenger**

To serve as intracellular messenger a compound must meet several requirements. Most important, its intracellular concentration must be very low and precisely controlled, so that short-lived transmembrane fluxes of the messenger would be able to change significantly its intracellular level—and thus modulate cellular mechanisms. In addition, it must bind selectively its substrate.

Because of the high coordination number and irregular coordination geometry that considerably enhance the specificity of its binding to biological molecules, Ca\(^{2+}\) ions could adequately meet these requirements and therefore could be established as
Fig. 1. A, Animal phylogenetic tree, based on data from Minkoff (1983). See also Woese (1987), for the relationship among the three urkingdoms (Archaeabacteria, Eubacteria, and Eukaryotes) and for their origin from the hypothetical universal ancestor. The scheme emphasizes animal groups whose channels have been studied more thoroughly. B, Evolution and phylogenetic distribution of ionic channels. The underlying view is that ionic channels evolved very early in the history of life, from a common hypothetical ancestor, the mechano-sensitive Ca channel, Ca(M). The evolutionary position and origin of several ionic channels are uncertain, and several missing links are postulated. Dashed and dotted lines are intended to reflect the current uncertainty regarding these evolutionary relationships. The channels in the elliptic boxes are hypothetical. C, Schematic representation illustrating the most likely sequence of evolution of the seven ionic channels described here. Ca(V) = voltage-activated Ca channel; K(Ca) = Ca-activated K channel; K(V) = delayed rectifier K channel; IK = inward rectifier K channel; Na(V) = voltage-activated Na channel; AChR = acetylcholine-activated endplate channel.
messenger and modulator of intracellular processes. Both the selection of intracellular molecular components sensitive to micromolar concentrations of Ca\(^{2+}\) ions and mechanisms for their fine intracellular regulation would follow. Transport mechanisms transferring Ca\(^{2+}\) ions outside the cell to lower \((\text{Ca}^{2+})_i\) would have been evolutionarily beneficial, as would a membrane less permeable to the ion to prevent its passive influx owing to the growing concentration gradient.

The cell was probably able now to regulate \((\text{Ca}^{2+})_i\)—and, consequently, cellular metabolism—by modulating the activity of the Ca transport mechanism associated with the membrane. This could have been the organization of the most primitive eukaryotes. Scarpa and Carafoli (1978) and Tada et al. (1978) may be consulted for excellent reviews on active transport of Ca\(^{2+}\) ions and cell function.

Was the First Ionic Channel a Ca Channel?

It probably was. In the previous paragraph we argued that the selection of an intracellular messenger probably preceded the appearance of ionic channels and that Ca\(^{2+}\) was the ion selected to this end. The following clues suggest that the first ionic channel was a Ca channel.

Active Ca transport (like all active transports) is a slow process that makes signals relying on transmembrane transport of the messenger Ca\(^{2+}\) ions particularly slow. However, because of the concentration gradient for Ca\(^{2+}\) ions that was due to the active Ca transport, much faster signals could be sent from outside the cell to its interior by Ca fluxes through passive-transport structures such as ionic channels.

The first channel with both selectivity toward Ca\(^{2+}\) ions and gating function—i.e., the capability to open and close—would have probably proved advantageous. Such passive structures, in the presence of a Ca gradient across the membrane, would have produced an equally precise but much quicker signal than would the active Ca transport. Alternative hypotheses that consider other types of channels as the primeval channel seem less probable. Na channels, for instance, seem to have appeared relatively late, as they are not found in lower animals such as Protozoa, Porifera, and Coelenterata. On the other hand, K channels, although considered very old, would have served no purpose if a K gradient across the membrane was not established. (This argument applies also to Na channels.)

At about this time, the interior of the cell had probably accumulated already a certain amount of membrane-impermeable macromolecules for cellular metabolism, each carrying several negative charges. This might have slowly drifted the resting membrane potential away from neutrality and established salt gradients. (In the eukaryotes studied so far, resting membrane potential ranges between \(-20\) and \(-90\) mV.)

Although a potential difference across the membrane was probably achieved by this time, the first Ca-selective channels could have very likely been gated by stimuli other than membrane voltage. Voltage-gated channels can in fact be operated only by a change of membrane potential—a far too slow process in these primitive organisms, relying as it does on translocation of charges (ions) across the membrane through active-transport mechanisms. More likely, therefore, these primitive Ca channels were directly activated by mechanical or chemical stimuli from outside. [Several mechano-sensitive Ca channels and other cation-selective channels, for instance, have been recently described (Brehm et al. 1984; Guharay and Sachs 1984, 1985; Lansman et al. 1987).] The cellular response, initiated by a rise in \((\text{Ca}^{2+})_i\) due to Ca\(^{2+}\) influx through Ca channels, would be terminated (i.e., low \((\text{Ca}^{2+})_i\)) would be reestablished) following both inactivation of Ca channels by entering Ca\(^{2+}\) ions (Brehm and Eckert...
1978; Kramer and Zucker 1985) and activation of energy-dependent Ca transport mechanisms by an increase of \((\text{Ca}^{2+})_i\) (Tada et al. 1978).

Then evolution probably selected membrane mechanisms for ion translocation that would permit a higher rate of signaling. This could be achieved by (1) replacing active transport systems with membrane channels capable of sustaining bigger and faster ionic fluxes, (2) shortening the response time by inactivation of Ca channels and by activation of Ca transport mechanism, and (3) maintaining very low \((\text{Ca}^{2+})_i\), so that a small and short-lived Ca influx can raise \((\text{Ca}^{2+})_i\) considerably.

Voltage-gated Channels

We suggested above that the first ionic channels were probably gated by stimuli other than voltage. In the membrane the presence of channels capable of producing quick and significant changes of membrane potential by passive ion fluxes made other forms of gating mechanisms possible. Voltage-gated channels probably appeared at this time, as a result of selection for faster signaling.

In addition to Ca channels activated by external stimuli, the cell probably shows now also voltage-gated Ca channels activated by membrane depolarization produced by Ca\(^{2+}\) influx through nonvoltage-gated Ca channels. Such a cell could have functioned as follows: when a mechanical stimulus involving only a small portion of the membrane hits the cell, a depolarization initially restricted to the stimulated area is produced by the activation of mechano-sensitive Ca channels and by consequent inward Ca flux. This depolarization subsequently extends to the entire cell membrane by voltage-gated Ca channels. The speed with which the depolarizing wave travels along the membrane depends on the density of voltage-gated Ca channels, in the same way as conduction velocity in most excitable cells of higher forms depends on the density of Na channels.

However, given the special function of Ca\(^{2+}\) as intracellular messenger and modulator of cellular processes, the density of Ca channels probably could not be increased considerably without compromising Ca modulatory functions. Thus the speed of the depolarizing wave sustained by inward Ca fluxes through voltage-gated Ca channels could have remained relatively low, although much higher than the diffusion of Ca\(^{2+}\) ions through the cytoplasm. Indeed, in the absence of voltage-gated channels, mechanisms solely based on Ca\(^{2+}\) diffusion through the cytoplasm from the stimulated area where Ca\(^{2+}\) influx occurs hardly ever would have been capable of satisfactory responses. In order for \((\text{Ca}^{2+})_i\), at the farthest point from stimulation to reach the required level for the response in a reasonable time, \((\text{Ca}^{2+})_i\) at the site of stimulation where Ca\(^{2+}\) influx occurs would probably be unbearably high.

This picture, as plausible as it may be, presents a major problem. The absence of repolarizing mechanisms implies that a cell depolarized by the influx of Ca\(^{2+}\) ions would remain in such a depolarized state until the slow active Ca transport system has extruded the excess cytoplasmic calcium. A depolarized membrane and a high \((\text{Ca}^{2+})_i\) seriously impair the regular functioning of the cell. While in such a state, the cell is not able to respond to other stimuli, thus making it unresponsive to the external environment.

Voltage-gated K channels of the delayed rectifier type, as we know them from higher organisms, might have appeared to repolarize the membrane. K channels would do so by opening in response to depolarization. Their opening, however, would take place with a certain delay with respect to voltage-gated Ca channels. This temporal shift in the activation of the two types of channels is the necessary requirement to avoid overloading of their opposite (depolarizing and repolarizing) effects on membrane voltage.
In this repolarizing task, K channels are very likely helped by K(Ca) channels, another type of K channel, a type that is activated by the binding of Ca\(^{2+}\) ions to the cytoplasmic side of the channel protein but that is also modulated by the membrane voltage. The K(Ca) channels thus open on a rise of (Ca\(^{2+}\)), and they close when the membrane repolarizes. K and K(Ca) can therefore be seen as a set of channels for reestablishing resting conditions and for determining the duration of the electrical response.

**K(Ca) Channel: an Evolutionarily Disputable Case**

The K(Ca) channel is somehow an unusual channel. Unlike most ionic channels, which are gated either by voltage or by a ligand, the K(Ca) channel is sensitive to both voltage and Ca\(^{2+}\) ions (Barrett et al. 1982). The relevant question here is whether, during evolution, voltage sensitivity preceded Ca\(^{2+}\) sensitivity, or vice versa.

K(Ca) channels are ubiquitous in excitable cells. Moreover, they also occur in evolutionarily primitive organisms such as Protozoa (Eckert and Brehm 1979) and Coelenterata (Anderson and Schwab 1982), suggesting their early appearance. Because very early in evolution cells could very likely change membrane voltage only slowly, whereas Ca channels were already present and some control of (Ca\(^{2+}\)) had been achieved, it is plausible to assume that Ca sensitivity appeared earlier than voltage sensitivity. The K(Ca) channel, with Ca sensitivity only, may have evolved from mechano-sensitive Ca channels (fig. 1B, dashed line). This view is supported by the evidence that (1) each of them is still sensibly permeable to the other ion and (2) both channels have Ca binding sites facing the cytoplasm (Eckert and Tillotson 1981). The primeval K(Ca) channel with only Ca sensitivity may have subsequently achieved voltage sensitivity when cells became able to produce large and rapid voltage changes across the membrane.

If, instead, K(Ca) channels developed voltage sensitivity first, then their appearance likely would have been delayed until cells were able to produce significant changes of membrane potential. In this case, the K(Ca) channel would have more likely evolved from a voltage-gated K channel and subsequently would have acquired Ca sensitivity (fig. 1B, dotted line). Although it seems reasonable to think that the K(Ca) channel derived from the voltage-gated K channel [the two channels are both voltage sensitive and K selective and show similar selectivity sequence (Hille 1973; Blatz and Magleby 1984)], the step that brought about the diversification—i.e., the acquisition of Ca sensitivity—might not have been simply a minor structural change. In fact, although both the selectivity sequence of the two channels and the sensitivity to blockers are similar (Armstrong and Binstock 1965; Bezanilla and Armstrong 1972; Hagiwara et al. 1976; Yellen 1984; Smart 1987), their conductances differ by more than one order of magnitude. This would suggest a major rearrangement of the selectivity filter of the channel, a rearrangement that probably took place in several steps.

**Paramecium: an Example of Channels at Work**

All types of channels described so far are already present in the ciliate *Paramecium*. The well-known example of how they work in organizing the typical avoidance response of this organism follows (Grell 1956; Eckert and Brehm 1979). When a cruising *Paramecium* hits an obstacle, it stops, reverses its swimming for a short while, then resumes the forward movement in a slightly different direction. This response is based on the electrical properties of its membrane and on the properties of the cilia, which move in one direction at low (i.e., \(<10^{-7}\) M) (Ca\(^{2+}\)), and in the opposite direction when (Ca\(^{2+}\)) is high (i.e., \(>10^{-6}\) M). Normally, when the *Paramecium* is swimming
forward, its membrane potential is at rest; the voltage is negative inside, and \((\text{Ca}^{2+})_i < 10^{-7} \text{M}\). When the \textit{Paramecium} hits an object, mechano-sensitive (Lansman et al. 1987) Ca channels are activated, and Ca\(^{2+}\) ions enter the cell, locally depolarizing the membrane. This induces progressively more-distant voltage-gated Ca channels to open, so spreading the depolarization to the entire cell membrane. Entering Ca\(^{2+}\) ions bind to the base of the cilia and induce them to reverse the beat and the direction of swimming. Backward movement continues until repolarization is achieved (by the combined action of delayed K and K(Ca) channels, which are activated by depolarization and by Ca\(^{2+}\) influx, respectively), and \((\text{Ca}^{2+})_i\) is lowered. With the reestablishment of resting conditions, the \textit{Paramecium} resumes its normal forward swimming.

**Toward the Na Channel**

The collection of channels present in \textit{Paramecium} endows this organism with adequate, although simple, responsive behavior. But living forms are not static. After \(\sim 3,000\) Myr of solely unicellular organisms, multicellularity appeared, bringing with it new demands. Among them, communication between cells and between various regions of the body was a major one. Excitable cells specializing to undertake this task were selected.

How did evolution work to generate the high speed of signaling that multicellularity required? In \textit{Paramecium} the propagation of the depolarization initiated locally by mechano-sensitive Ca channels is sustained by voltage-gated Ca channels. An increase in the density of Ca channels, which would increase the speed of the depolarizing wave, would have very likely been evolutionarily favorable. But a high density of Ca channels would have compromised the central role of Ca\(^{2+}\) ion as modulator of intracellular functions. It would not be beneficial for the cell to have a large influx of Ca\(^{2+}\) ions that would alter all cellular processes modulated by that ion every time a signal passes. A distinction needs to be made, however, with respect to muscle fibers in which the major function of contraction takes place on activation of contractile proteins by Ca\(^{2+}\) ions.

In primitive muscle fibers—and, more generally, in primitive cells with contractile properties—all the activating Ca\(^{2+}\) ions for contraction probably came from outside the cell, and a high density of Ca channels in the membrane would have been doubly advantageous. It would increase the speed of the depolarizing wave along the fiber and at the same time would speed up the activation of the contractile machinery, as result of the greater influx of Ca\(^{2+}\) ions and the consequent more rapid increase in \((\text{Ca}^{2+})_i\). Probably because of this coincidence of advantages, in primitive muscle fibers the number of Ca channels in the membrane increased. The giant muscle fibers of certain crustacea (crabs and barnacles) exemplify the capability of these membranes to conduct the depolarizing wave by Ca channels and to provide an inward pathway for Ca\(^{2+}\) ions which, with those coming from intracellular stores, contribute to the activation of contractile proteins (Fatt and Ginsborg 1958; Hagiwara and Naka 1964; Caputo and Di Polo 1979).

Strategies other than increasing the density of Ca channels in the membrane were selected, however. The appearance of Na channels, capable of carrying greater ionic fluxes across the membrane without interfering with intracellular processes, would have been evolutionarily favorable. Since in axons there is no instance of action potentials propagating through Ca channels, evolution in nerve cells probably worked more effectively and began earlier in selecting Na channels to sustain potential changes. In muscle fibers, instead, the selective advantages of Na channels in the control and propagation of action potentials were probably less pronounced when compared with
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those of Ca channels. Benefits from Na channels increased, however, when intracellular stores (mainly sarcoplasmic reticulum) were achieving more importance in supplying Ca ions for muscle contraction (Franciolini 1985).

The conversion from Ca-dependent to Na-dependent depolarization was probably very slow, and indeed it is not entirely completed yet. There are in fact several instances in which Ca channels coexist with Na channels and variously contribute to the electrical excitability. In the flight muscle of the fly Sarcophaga bullata, for instance, the action potential is produced by an increase of the membrane’s permeability to Ca\(^{2+}\) ions, although a contribution of Na\(^+\) to the electrical response has been shown (Patlak 1976). Other conspicuous examples of electrical responses consisting of Na-dependent and Ca-dependent components can be found in the nerve cell of the mollusk Aplysia (Geduldig and Junge 1968) and in smooth and cardiac muscle of vertebrates (see Hagiwara 1983).

The result of this conversion was a higher speed of conduction, mainly owing to the considerable advantage that Na channels have over Ca channels: unlike Ca\(^{2+}\) ions, Na\(^+\) ions do not interfere with any of the cellular processes, so that the number of Na channels in the membrane—and thus the density of inward current generated—could be greatly increased. For instance, when similar extracellular concentrations of Na\(^+\) (140 mM) and Ca\(^{2+}\) (100 mM) are used, the maximum-density current through Na and Ca channels of frog muscle is \(\sim 3\) mA/cm\(^2\) (Hille and Campbell 1976) and \(\sim 30\) \(\mu\)A/cm\(^2\) (Almers et al. 1981), respectively. Since the conductance of Na and Ca channels is similar, on the order of 10 pS (Patlak and Horn 1982; Reuter et al. 1982), the density of Na and Ca channels is \(\sim 300/\mu\)m\(^2\) and \(\sim 3/\mu\)m\(^2\), respectively. [Some of these values are supported by more direct evidence (Fenwick et al. 1982; Reuter et al. 1982; for Na channel density, see Hille 1984).]

The density of Na channels reported above has been shown to represent the optimum density, with respect to the speed of propagation of the action potential. A further increase of Na channel density would in fact decrease the speed of propagation because the additional current density generated by the extra channels would not compensate any longer the opposite-going current produced by the translocation of gating charges within the membrane (Hodgkin 1975).

The AChR Channel

A final aspect of the evolution of ionic channels is the origin of the channels responsible for chemical transmission of impulses at the synapses. The most important feature of these channels is that they are all gated by ligands and are insensitive to voltage. Although they differ in the transmitter that activates them (ACh, glycine, or GABA), as well as in kinetics, selectivity sequence, and conductance, they nonetheless show several similarities—e.g., gating by ligands, insensitivity to voltage, and polymeric structure—that suggest their common origin. Their ancestor probably appeared simultaneously with the process leading to multicellularity. The likely candidate was the AChR channel that is already found in Platyhelminthes and Nematoda (Byerly and Masuda 1979; Koopowitz and Keenan 1982), two of the earliest multicellular groups.

Besides the presence of AChR channels in evolutionarily old organisms, other observations favor this view. Glycine- and GABA-receptor channels, for instance, are both anion selective (Borman et al. 1987). Although we have not addressed the question of how and when anion selectivity appeared, it seems that cation selectivity preceded anion selectivity and that for a long time it was the only channel selectivity present. An additional argument in support of this view may be the functional difference
between the cation-selective AChR channel and the glycine- and anion-selective GABA receptor channels: the former has an activating function, which, it is reasonable to assume, preceded the modulatory (inhibitory) function of the latter.

There is no clear functional evidence that transmitter-activated channels are evolutionarily related to voltage-gated channels. Transmitter-activated channels usually have considerably large pores, are scarcely selective, and are insensitive to voltage. However, certain structural similarities between the AChR and Na channel are worth mentioning. The AChR channel is a pentamer protein composed of four structurally similar subunits (Raftery et al. 1980), each coded by a separate gene. The carboxy-terminal portion of each AChR subunit presents four hydrophobic, membrane-spanning segments (M1–M4) (Noda et al. 1982, 1983a, 1983b, 1983c) consisting exclusively of uncharged amino acid residues. Moreover, the four subunits exhibit such similarity of both sequence and predicted secondary structure as to suggest that the genes encoding them descended from a single common ancestor by gene duplication (Noda et al. 1983b).

Unlike the polymeric AChR channel, the Na channel consists of a single polypeptide chain about four times as large as any of the AChR subunits (Noda et al. 1984). However, the monomeric Na channel protein contains four domains, each analogous to a single subunit of the polymeric AChR channel; that is, each of these domains shows the characteristic pattern of alternating hydrophobic and hydrophilic regions that are interpreted as five membrane-spanning helices, in a manner very similar to that of the M1–M4 segments of the AChR channel monomers. This finding suggests that these hydrophobic intramembrane domains of the Na and AChR channels derive from a common ancestor by internal duplication of genes (Noda et al. 1984). This suggestion is weakened by the fact that the two channel proteins do not possess the sequence similarity expected on the basis of that hypothesis.

Since structural similarities between the AChR and Na channels are not striking, and since functional similarities are weak, it is not possible to say whether the AChR channel evolved from the Na channel—possibly as result of duplication of genes coding for these channel proteins—even though such a duplication appears to be a relatively common phenomenon.

Other possibilities, such as phylogenetic independence of the AChR and Na channel or phylogenetic relationships of the AChR channel with channels other than Na—will not be considered here, owing to total lack of evidence.

Conclusion

The paucity of data available on ionic channels of primitive organisms prevents a proof of the above view on the evolution of membrane channels. However, the overall picture of channel evolution, illustrated in the phylogenetic tree of ionic channels that is shown in figure 1B, is plausible. Support includes (1) the Ca channel as the primeval ancestor of the existing ionic channels and (2) the diversification of Na, K, I_K, K(Ca), and Ca channels before Protostomes and Deuterostomes diversified (they show the same collection of ionic channels). These ideas will be tested when a more detailed survey of channel distribution is done in more animal groups, as well as when the primary structure of the major channels becomes available.

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