“Evolution of sodium channels predates the origin of nervous systems in animals”
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NaV Channel, α subunit

Gymnotiformes

Mormyriformes
Prediction 3: Selection should have acted specifically on target regions of Scn4aa with functional consequence for EOD waveform.

How did animals evolve?
From Single Cells to a Vast Kingdom

From single celled ancestors, millions of descendant multicellular animals, in the geological period known as precambrian.

Origin of animals was ~1,000 MYA.

Oldest fossil: Adam Maloof (Princeton) found sponge like multicellular fossils in Australia. In 635 MY old oil deposits, cholesterol from sponges.

Precambrian explosion (~600 MYA).

Recent evidence from genomes finds chemical sequences found in multicellular animals long before multicellularity.

Examples: Cephasporea owczarzaki (choanoflagellates) a single cell parasite of snails.

With an international genome sequencing project started in 2007, much is now known about the early ancestors of multicellular animals.

Which organisms have nervous systems?

Animals (except sponges and placozoans)

Sponges are multicellular, but lack a nervous system

Placozoans are multicellular but lack nervous system

Placozoan body plan and reproduction.

Placozoan phylogeny from whole genome analysis

Bayesian phylogeny of metazoans places Trichoplax as the sister group to cnidarians and bilaterians. Maximum parsimony applied to the same alignment results in a single tree with the same topology shown here. Posterior probabilities are reported above each branch; likelihood bootstrap support values are reported below.

Sequencing and analysis of the 98 million base pair nuclear genome of the placozoan Trichoplax adhaerens. Whole-genome phylogenetic analysis suggests that placozoans belong to a ‘eumetazoan’ clade that includes cnidarians and bilaterians, with sponges as the earliest diverging animals.
Earliest long distance, targeted, and rapid communication via electrically excitable cells is seen earliest in cnidarians, and in bilaterian animals. Action potentials required. 

$Na_v$ ion channels 

$Ca^{++}$ channels are found in single celled protozoa (Paramecium) are used for intracellular signaling. 

Hypothesis: $Na_v$ channels evolved from $Ca^{++}$ channels for intercellular signals that did not interfere with intracellular signaling.

Where did the authors obtain their data for this study? i.e. how did they obtain gene sequence data for all of the species they used?

Genome databases used in this study

Animals with nerve nets

Nematostella vectensis, an anemone.


Mnemiopsis leidyi, a ctenophore

Trichoplax adhaerens – placozoan

Amphimedon queenslandica - Sponge

1.1 Billion Years of Evolution Produces Three (4?) Superfamilies of Ion Channels

Choanoflagellates: unicellular protist

Monosiga brevicollis


Evolution of Voltage-gated channels

Primitive K+ channel from bacteria is composed of 4 identical subunits, each with three alpha helices of which two are transmembrane domains (red and blue on left).

By contrast, voltage gated channels are composed of a tetramere of six TM-alpha helicies

Another K channel has two repeats of an inward rectifying K+ channel. Two of these are thought to form a channel with 4 p-loops.

What are the main functional differences between voltage activated sodium channels and voltage activated calcium channels at protein structural level?

Hypothetical Na, structure with 4 domains. Liebeskind et al (2011)
Goals of this study

- Find voltage-gated ion channel genes in basal animals + unicellular ancestors.
- Analyze evolutionary history of the genes for \( \text{Na} \) and \( \text{Ca} \).
- Explore pore motif (for ion selectivity)
- Explore inactivation gate
Choosing flagellates have Na channels

But they don't have a nervous system.

...and they aren't multicellular.

Monosiga brevicollis

Structure of the Na channels

Open reading frame of mRNA transcript sequenced for Monosiga, and partial transcripts from Trichoplax, so the Na genes are expressed.

The pore contains D/E/E/A motif in both species.
(Intermediate between Ca and Na as seen in other invertebrates too)
Domains: Trichoplax beta is incomplete (only 3 domains)

Human Na, 2.1

The 7.2-kilobase cDNA sequence, designated hNav2.1, predicts a 1682-amino acid protein that bears 52%, 49%, and 46% overall identity with sodium channels cloned from rat brain, skeletal muscle, and heart, respectively. Until recently, all cloned vertebrate voltage-dependent sodium channels exhibited high sequence homology to one another and appeared to comprise a single multigene subfamily. An exception is the human Nav2.1 channel proposed to represent a second Na channel (NaCh) gene subfamily since comparison with previously cloned voltage-gated NaChs revealed only 40-45% identity.

Positively charged S4 segments are present in hNav2.1, but there are fewer basic residues in repeat domains 1, 3, and 4 than in other cloned sodium channels.

Nav2.1 is prominently expressed in both heart and uterus. mNav2.3 mRNA was most abundant in heart and uterus, and the transcript levels in heart, brain, and skeletal muscle were differentially regulated during development.

Brugada syndrome, first described in 1992, has a high risk of sudden cardiac death. Nav2.1 was strongly expressed in the hearts of patients with Brugada syndrome.

http://channelpedia.epfl.ch/ionchannels/129
Sodium Channel Evolution

Study confirms the presence of ion channels in choanoflagellate and placozoan that match the key elements of Na channels in animals.

- Have both the pore domain and the inactivation domain similar to Na channels.
- Alternative hypothesis is that these channels are closer to other channels, not Nav.
- The results of this study suggest that Nav existed before multicellularity, before animals.
- The paper also suggests that these Nav channels were derived from Cav channels.
- Shows that function is coopted from existing gene rather than waiting for a new gene, new function.

The placement of sponges/cnidarians and bilaterians is consistent with other studies, the placement of ctenophores (have a nervous system) outside of placozoans, cnidarians, and bilaterians suggest that placozoans lost the nervous system.

Loss of Nav in sponge, may reflect loss of function during sedintary life style.

CONCLUSIONS

Since 2011 another Na channel phylogeny traced to common ancestor of fungi and animals


The supergroup Opisthokonta includes fungi and animals. Obviously animals have nerves and muscles, and fungi don’t. What about Na channels?

Sodium Leak Channels (NaLCN) Sodium, Leak, non-selective are 4 x 6TM domain Na channels which have no voltage sensitivity. For example, NALCN can cause a cell to become slightly depolarized so that it fires repetitively.

Previous studies: showed that NALCN diverged from voltage gated channels before Cav and Nav diversified. Fungi have Ca channels with some similarity.
Bibliography


