Trends in Neurosciences

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Review

Back to the Basics: Cnidarians Start to Fire

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The nervous systems of cnidarians, pre-bilaterian animals that diverged close to the base of the metazoan radiation, are structurally simple and thus have great potential to reveal fundamental principles of neural circuits. Unfortunately, cnidarians have thus far been relatively intractable to electrophysiological and genetic techniques and consequently have been largely passed over by neurobiologists. However, recent advances in molecular and imaging methods are fueling a renaissance of interest in and research into cnidarians nervous systems. Here, we review current knowledge on the nervous systems of cnidarian species and propose that researchers should seize this opportunity and undertake the study of members of this phylum as strategic experimental systems with great basic and translational relevance for neuroscience.

Trends

Accumulating genomic data strongly support the position of Cnidaria as the sister clade to Bilateria. The emergence of a simple nerve net together with biological, structural and functional diversity within this taxonomic group make cnidarians highly informative for comparative approaches.

Recently sequenced genomes and transcriptomes provide insights into the molecular complexity of cnidarian nerve nets. The diversity of synaptic proteins, small neurotransmitters, neuropeptides, and their processing machinery and receptors, is comparable with that of chordates.

Recent advances in imaging and gene manipulation techniques make cnidarians now amenable to functional analysis addressing molecular, behavioral and evolutionary questions.

Accumulating evidences point to multiple roles of the simple nervous systems. Emerging evidence points to functions of nervous systems beyond simple sensory and motor coordination.

The Power of a Comparative Approach to Understand Neural Circuits

Since the time of Cajal, comparative approaches have been powerful tools in neuroscience [1]. However, in contrast to Cajal and Sherrington's ‘neuron doctrine’, which established that the individual neuron is the functional unit of the nervous system [2], modern neuroscience is now focused on understanding entire neural circuits, as they may have multicellular responsible for emergent functional properties [3]. With the advent of innovative methods, researchers expect to record and manipulate entire neural circuits. This could generate a dynamic picture that will reveal, perhaps for the first time in depth, how complex neural circuits generate behavior and internal functional states.

The immense complexity of the human brain, consisting of a hundred billion neurons of a yet unknown number of different types, with each neuron able to connect to tens of thousands of other neurons, makes a holistic understanding of how the system works, or how neuronal circuits work on a scale of the entire nervous system of an organism, extremely challenging. Therefore, there is a need to study alternative models with smaller and simpler nervous systems.

Examples of the strength of this comparative approach in neuroscience in the 20th century include the use of invertebrate models, such as the marine mollusc *Aplysia californica*, to elucidate mechanisms of neural function that specifically mediate habituation, sensitization, and forms of associative learning [4]. The large neurons of *Aplysia* allowed the detailed examination of neuronal architecture, physiology, and control of behaviors at the level of single well-characterized cells and defined signaling pathways. Other classical examples of breakthroughs that were made possible by using a comparative approach include the understanding

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of the ionic basis of the action potential (squid) [5], the discovery of adult neurogenesis (canary) [6], conditioned reflexes (dog) [7], and the earlier discovery of dendritic spines (chicken) [8]. More recently, significant advancements in temporal control of neuronal function through optogenetics have been made thanks to the characterization of channel-rhodopsins in algae [9].

In contrast to the comparative tradition in neuroscience, the power of molecular genetics has driven the exploitation of a selected group of model organisms, particularly *Caenorhabditis elegans*, *Drosophila melanogaster*, *Xenopus*, zebrafish, and mice. Without doubt, these model organisms have revolutionized our understanding of biological processes. At the same time, particularly for neuroscience, the emphasis on small number model organisms has come at the cost of essentially ignoring the rich structural and functional diversity of nervous systems in the animal kingdom. This situation arose due to the difficulty of applying genetic or molecular methods to most species, thereby leaving them outside the reach of molecular neuroscience.

This outlook has changed dramatically in the last few years due to the introduction of molecular genetics that can be applied to a wide variety of species. In many of these cases, it was the Human Genome Project [10] that opened the way for systematically sequencing genomes of representatives of every animal phylum. Every area of biology has been transformed by the development of sequencing technologies and transgenics. This, together with gene-editing techniques such as CRISPR/Cas9 [11], have led to a ‘democratization’ of molecular biology, with functional and genomic analyses now possible in a wide range of species. A similar case can be made for the use of calcium imaging of neural circuits [12], which has enabled access to functional information from neurons that were previously too difficult to record from with electrical methods. Taken together, these advances have led to a renewed interest in studying nervous system evolution, structure, and function, by using non-traditional model animals with simple nervous systems. Such investigations are now not only possible, but also appear necessary for understanding the structural determinants of behavior in more complex animals.

In the following, we briefly review some of the basic features of the neurobiology of various cnidarians and then illustrate some examples of how modern techniques are starting to yield significant insights into their nervous systems. We end with a ‘call to arms’, pointing out the unique opportunities and potential benefits if we add basal metazoans to the neuroscience menu.

The Earliest Nervous Systems Were Present in the Common Ancestor of Cnidaria and Bilateria

If one aims to understand how nervous systems function by identifying cardinal shared features of neurons and neural circuits via the comparative approach, it is essential to study the earliest evolutionary examples. Remarkably, nervous systems appeared very early in animal evolution and were certainly in place prior to the origin of bilaterally symmetric animals – also known as Bilateria (Figure 1). Of the lineages that diverged prior to the bilaterian radiation, nervous systems are present only in Ctenophora and Cnidaria. Intriguingly, while cnidarian and bilaterian nervous systems have many characteristics in common, those of Ctenophora appear to differ fundamentally – for example, glutamate and neuropeptides may be the sole neurotransmitters used [13]. But, in addition to the controversial phylogenetic position of Ctenophora [14,15], a paucity of data and limited amenability to technical approaches currently make these animals difficult candidates for comparative studies of neurobiology. A more practical choice for such studies are cnidarians, a phylum of ~11 000 aquatic animals that occupies a strongly supported position as the sister clade of Bilateria (Figure 1). Cnidarians, which include jellyfishes and polyps and are characterized by their nematocytes (stinging cells), have long been utilized in laboratories as experimental organisms to address diverse biological questions [16–20].

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