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Evolutionary origin of the nervous system from Ctenophora prospective

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Abstract

Nervous system is one of the key adaptations underlying the evolutionary success of the majority of animal groups. Ctenophores (or comb jellies) are gelatinous marine invertebrates that were probably the first lineage to diverge from the rest of animals. Due to the key phylogenetic position and multiple unique adaptations, the noncentralized nervous system of comb jellies has been in the center of the debate around the origin of the nervous system in the animal kingdom and whether it happened only once or twice. Here, we discuss the latest findings in ctenophore neuroscience and multiple challenges on the way to build a clear evolutionary picture of the origin of the nervous system.

KEYWORDS

comb jelly, ctenophora, evolution, nervous system, neuron

1 | INTRODUCTION

Among all multicellular organisms, only the animal kingdom possess a nervous system, a mechanism allowing quick adjustments of individuals to the ever-changing environment. Nervous system is one of the key adaptations underlying the evolutionary success of the vast majority of animal taxa. Along with some derived parasites like myxozoans, the only animal lineages that lack neurons are sponges and placozoans, while groups of Ctenophora (or comb jellies), Cnidaria (e.g., sea anemones, jellyfish, and corals) and Bilateria (the majority of animals, including insects, vertebrates, and worms) have nervous systems. Thus, understanding the mechanisms of nervous system origin is important for building a precise picture of evolution in the entire animal kingdom. However, it is also important to keep in mind that the nervous system is not the only possible way to succeed in the evolution as, for example, neuronless sponges have evolved alternative survival strategies such as filter-feeding, high regeneration capacity, and spicule-based defense against predators.

While a wide morphological diversity of nervous systems can be observed among animals (Martín-Durán & Hejnol, 2021), they all share the main building block, a cell type called "neuron." The nervous system in Ctenophora and Cnidaria is not centralized (e.g., lacking a brain) however it includes multiple types of neurons and sensory cells forming networks and specialized sensory structures (e.g., aboral organ, see below). Even though cognitive abilities of ctenophores have not been characterized at all, it is known from Cnidaria that a diffuse nerve net is enough to support some forms of learning, such as habituation, sensitization, and associative learning (Barron et al., 2023; Bielecki et al., 2023; Botton-Amiot et al., 2023). Thus, expanding neuroscience research to Ctenophora, that were either the first or second lineage to diverge from the rest of animals over

600 million years ago, will shed light not only on the origin of nervous system in the animal kingdom but will also reveal the principles behind processes traditionally attributed to centralized nervous systems.

Interest in neuroscience is historically driven by human health concerns and a natural desire to understand how the brain works. Therefore, the majority of studies have been focused on mammalian brains and organisms that in some way model the human brain (e.g., mice and rats, other vertebrates, and to a somewhat lesser extent, drosophila and *Caenorhabditis elegans*) creating a knowledge void in understanding the nervous system of Ctenophora and perception of it as "simple" (Arendt & Reznick, 2008). This in turn leads to a lack of scientific attention towards this apparently "simple" nervous system. However, such arguments around complexity should not be considered as a valid reasoning when prioritizing research as still there is no scientific consensus about a precise definition of biological complexity and ways of measuring it. It has also become clear that complexity is a multi-dimensional concept, which, in addition to the number of parts (e.g., the number of neurons in a nervous system) includes for example flexibility at different biological levels (e.g., multifunctionality, resilience to environmental stress, or regenerative capacity of neurons) (Koch & Laurent, 1999; Rebout et al., 2021). Thus, as you will see below, a seemingly "simple" nervous system of Ctenophora is not that easy to understand and it even makes us reconsider some of the key views of neurobiology.

1.1 | What is a neuron and do ctenophores have them?

1.1.1 | How do we define a neuron?

Generally speaking, neurons are cells sensing the environmental cues and transmitting the information throughout the animal body. Typical neurons as we know from bilaterians are highly polarized cells with long projections, dendrites, and axons, connected through synapses (Jékely, 2021; Rolls & Jegla, 2015). However, this idea of neurons is very narrow as it does not fit a range of sensory-neurosecretory cells deprived of long neurites and synapses as well as neurons of ctenophore and cnidarian nerve net that appear to lack axodendritic polarity (Burkhardt & Jékely, 2021; Burkhardt et al., 2023; Jekely et al., 2015; Jékely, 2021; Stone, 2020). Thus, due to the high diversity of neuronal functions, physiology, morphology, and molecular composition within and between different taxa, clearly defining a neuron is quite challenging (Kristan, 2016). The recent literature on this topic suggests that neurons are polarized secretory cells signaling through electric impulses and chemical transmitters, and they may be equipped (but not necessarily) with long projections (Burkhardt & Jékely, 2021; Jekely et al., 2015; Moroz, 2021).

1.1.2 | Ctenophore biology

Ctenophores (or comb jellies) are gelatinous marine animals, mostly planktonic (Haddock, 2004), even though there are some benthic species (Glynn et al., 2019). These animals got their name due to the combs—giant ciliary structures that they use for locomotion (Figure 1a). Ctenophora is a largely understudied group, and most of the microscopy, molecular, and physiological data come from *Mnemiopsis* (Lobata), *Pleurobrachia* (Cydippida), and *Beroe* (Beroida) (Hayakawa et al., 2022; Hernandez-Nicaise, 1991; Jager et al., 2011; Moroz et al., 2014; Sachkova et al., 2021; Sebé-Pedrós et al., 2018) that have been available to scientists due to their common presence in shallow coastal waters (Babonis, 2018). The majority of ctenophore species appear to inhabit the deep sea though and are still awaiting proper scientific characterization (Ford et al., 2020; Haddock, 2004). Due to the high ecological plasticity of *Mnemiopsis leidyi*, it has become an important invasive species that colonized a wide range of marine environments and disrupted native ecosystems (Burton, 2008). Such a plasticity along with high regenerative capacity (Edgar et al., 2021) probably explains why *M. leidyi* has become a lab model organism (Martindale, 2022) that can adapt to the artificial conditions of aquarium facilities and be successfully cultured and reproduced over multiple generations (Presnell et al., 2022; Soto-Àngel et al., 2022).

Ctenophores have many peculiar anatomical features including for example rotational symmetry and transient anus (Dunn et al., 2015; Tamm, 2019). Comb jellies are built of ectodermal and endodermal epithelial layers with a thick layer of gelatinous mesoglea between them and thus are considered as diploblastic, even though muscle and neuronal cells are present in their mesoglea too (Burton, 2008). Ctenophores have evolved a variety of body plans (Figure 1a): cydippid (rounded body with two long tentacles, e.g., *Pleurobrachia*), lobate (two large lobes next to the mouth and reduced tentacles, e.g., adult *Mnemiopsis*), atentaculate (no tentacles or lobes, e.g., *Beroe*), platyctenid (flat with long tentacles), and ribbon-like (e.g., *Cestum*) (Whelan et al., 2017). The main body axis of ctenophores goes through the mouth on one end and aboral sensory organ on the opposite side; anal pores

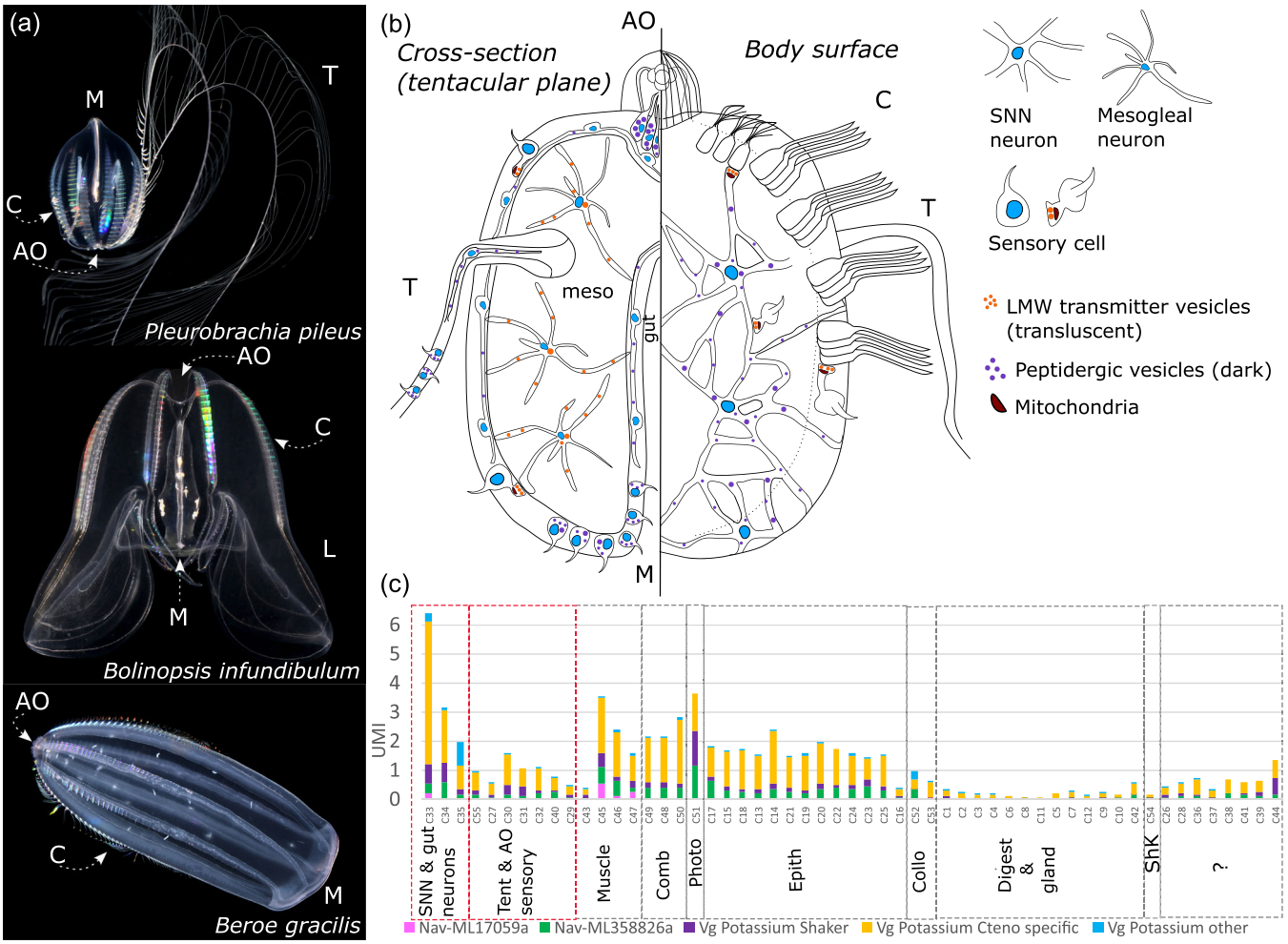

FIGURE 1 Ctenophore body plans and nervous system. (a) Examples of ctenophore species with different adult body plans: cydippid *Pleurobrachia pileus*, lobate *Bolinopsis infundibulum*, and beroid *Beroe gracilis*. Photography and identification by Joan J. Soto-Angel (University of Bergen). (b) Schematic of ctenophore nervous system; the details of anastomosed SNN, mesogleal neurons, and sensory cells are shown as described in early cydippid larva of *Mnemiopsis leidyi* (Burkhardt et al., 2023). The left side of the larva is shown as a cross-section through tentacular plane, while the right side is showing the body surface. Synapses are shown with low molecular weight (LMW) neurotransmitter vesicles and mitochondria inside. In (a) and (b), AO—aboral organ; M—mouth; C—combs; T—tentacles; L—lobe; and meso—mesoglea. (c) The highest expression of genes encoding for voltage-gated (Vg) ion channels is observed in ctenophore SNN (C33 cluster). The bar plot shows summed-up UMI values for two sodium channels (Nav), 11 potassium channels from Shaker family (Vg Potassium Shaker), 27 potassium channels from a ctenophore-specific clade (Vg Potassium Cteno specific), and five unclassified potassium channels (Vg Potassium other) (Li et al., 2015) measured by whole-body single-cell RNAseq study in *M. leidyi* (Sebé-Pedrós et al., 2018). The annotation of cell clusters (shown as C33, C34, C35, etc. on *X*-axis) is according to (Babonis, 2018; Sachkova et al., 2021; Sebé-Pedrós et al., 2018). Note that mesogleal neurons and sensory cells on the body surface have not been annotated yet. AO, aboral organ; Collo, colloblasts; Digest, digestive; Epith, epithelium; SNN, subepithelial nerve net; Tent, tentacle; UMI, unique molecular identifier.

transiently open to eliminate undigested food that remains right next to the aboral organ (Tamm, 2019).

Interestingly, all the studied ctenophores apart from Beroida have a cydippid morphology at larval stage, and later in the life cycle some species metamorphose into lobate, ribbon-like, or platyctenid adult, while some stay as cydippids (Glynn et al., 2019; Soto-Angel et al., 2023). That is in line with the fact that the last common ancestor of extant ctenophores that lived around 350 million years ago was a cydippid (Whelan et al., 2017). The life cycle of ctenophores is still being debated. On the one hand, many ctenophores have two morphologically distinct life stages (cydippid followed by lobate or platyctenid) occupying distinct ecological niches suggesting that they can be considered as indirect developers with a cydippid larval stage (which is however able to spawn—so-called "larval reproduction") (Soto-Angel et al., 2023). On the other

hand, they start spawning very early in life and continue until metamorphosis to restart again as adults evidencing for the direct development (Edgar et al., 2022). Here, we will stick to the tradition and will refer to the early cydippid life stage as larva. Nearly, all the studied ctenophore species are hermaphrodites, and while self-fertilization is possible (Ford et al., 2020), ctenophores have strategies to increase chances of cross-fertilization through communication by chemical factors released in water (Sasson et al., 2018) that they probably detect with multiple sensory cells on their body surface (see below). Interestingly, some benthic ctenophores brood their larvae and are able to reproduce asexually by fragmentation (Glynn et al., 2019).

Tentacles of comb jellies are enriched with specialized secretory cells and colloblasts, producing adhesive compounds (Hernandez-Nicaise, 1991), probably of proteinaceous nature (Babonis, 2018), that enable ctenophores to capture their prey. Beroids, on the other hand, have no tentacles and colloblasts and prey on other ctenophores by completely engulfing them or biting off small pieces with their macrociliary teeth (Hernandez-Nicaise, 1991). All the known ctenophores are carnivorous (Haddock, 2007), and with this feeding strategy having a nervous system appears particularly advantageous as it allows actively detecting and catching the prey. Coincidently, this is in line with carnivorous cnidarians having neurons too and neuron-less filter-feeder sponges and placozoans grazing on microorganisms in biofilms (Feuda et al., 2017). Evolution of more complex sensory and neuronal structures in connection to the carnivorous lifestyle has been proposed in several groups of bilaterians (e.g., eyes in arthropods) and has been discussed as a general mechanism that triggered the early evolution of nervous system during the "Cambrian explosion" (around 540 million years ago) (Budd, 2015; Monk & Paulin, 2014).

While some of ctenophore cell types sound familiar to all the biologists (e.g., muscles, neurons, epithelial and digestive cells), comb jellies also have multiple unique innovations such as colloblasts, comb cells, and motile macrociliary "teeth" of Beroe (Hernandez-Nicaise, 1991). The single-cell transcriptomics study identified 55 cell clusters (roughly corresponding to cell types) in the whole body of adult *Mnemiopsis*, and epithelial, digestive, muscle, photocyte, and comb cells were annotated based on the similarity of enriched genes to known bilaterian genes (Sebé-Pedrós et al., 2018). Further complex comparisons between ctenophore species with and without collobalsts allowed annotating colloblast cell cluster too (Babonis, 2018). However, the large portion of cell clusters could not be annotated based on the enrichment of bilaterian homologs (Sebé-Pedrós et al., 2018), and neuronal cell types were identified only with the discovery of ctenophore-specific neuropeptides that were used as highly specific neuronal markers (Hayakawa et al., 2022; Sachkova et al., 2021). Keeping in mind the long evolutionary time since the split of the ctenophore lineage from the rest of animals (>600 million years ago) and the number of their unique adaptations makes the multiple unusual features of their neurons slightly less surprising.

1.1.3 | Ctenophore nervous system

Ctenophora have a diffuse nervous system composed of a subepithelial nerve net (SNN), mesogleal neurons, and multiple sensory cells (Figure 1b) (Hernandez-Nicaise, 1991). Ctenophores also have a sensory aboral organ equipped with a unique statocyst controlling the position of their body (Tamm, 2014) and putative mechano- and photo receptors coming in contact with the SNN (Aronova, 1974). Neurons are also present within tentacles (Jager et al., 2011; Sachkova et al., 2021). SNN is located under the epithelium and is built of multipolar neurons (Hernandez-Nicaise, 1991). In adult ctenophores, the SNN appears as a polygonal network with each edge composed of a bundle of several neurites ("nerve cords") (Jager et al., 2011; Norekian & Moroz, 2020). Not all the neurons make part of the polygonal network though (Jager et al., 2011; Norekian & Moroz, 2019). In young cydippid larvae, the nerve cords and polygonal network have not been observed; on the contrary, the SNN is built of multiple individual neurons with long highly branching neurites (Burkhardt et al., 2023; Sachkova et al., 2021) (Figure 1b). Surprisingly, neurites of a cydippid neuron are anatomosed (i.e., directly fused) with each other and with other SNN neurons forming a syncytium (Burkhardt et al., 2023; Sachkova et al., 2021) suggesting that neuronal excitation is directly transmitted between different neurons of SNN. This syncytial nerve net is an exception from the neuron doctrine by Ramón y Cajal stating that nervous system is built from separate cells (Burkhardt et al., 2023). The developmental mechanism underlying the formation of the adult "nerve cords" and polygons from the larval syncytial SNN is still unclear. It is also unknown if anastomoses between neurites observed in *Mnemiopsis* larvae persist in adult life stage and in other ctenophore species. While synapses bearing clear vesicles can be found between the SNN neurons and sensory cells, no synapses have been detected between different neurons

of the SNN or with mesogleal neurons (Burkhardt et al., 2023). SNN neurons produce a dozen of neuropeptides packaged into electron-dense vesicles distributed between the cell bodies and neurites (Sachkova et al., 2021). Mesogleal neurons are multipolar and form a loose mesh in the mesoglea (Jager et al., 2011). Unlike the SNN neurons having electron-dense vesicles, mesogleal neurons are filled with clear vesicles, that are bigger in the cell bodies and smaller in their long nonbranching processes (Burkhardt et al., 2023). While chemical or electrical synapses between mesogleal neurons and SNN have not been detected, it appears that they come into physical contact (Burkhardt et al., 2023).

Within the nervous system, synaptic contacts are present between diverse sensory cells and the SNN, mesogleal neurons, and comb cells (Burkhardt et al., 2023). Neuroeffector synapses can be found in diverse cell types including gland cells, photocytes, colloblasts, muscles, and ciliated groove cells (control the beating of combs) (Hernandez-Nicaise, 1991; Sachkova et al., 2021) suggesting neuronal control of their function. Ctenophore synapses have a unique structure: a so-called triad built of clear synaptic vesicles, endoplasmic reticulum, and a mitochondrion (Hernandez-Nicaise, 1973). Importantly, these elements have a very specific spatial distribution within a synapse, where a cistern of smooth endoplasmic reticulum is sandwiched between a mitochondrion and a single layer of synaptic vesicles. While the triad has not been reported in bilaterians and has been discussed as one of the key unique ctenophore features (Moroz & Kohn, 2015), it was reported in a cnidarian jellyfish (Anderson & Grünert, 1988). Moreover, both mitochondria and endoplasmic reticulum can be found in the synapses of bilaterians as well (Devine & Kittler, 2018; Kuijpers et al., 2023) suggesting that there might be similarities in how these synapses work. In addition to commonly known asymmetrical (or polarized) synapses where pre- and postsynapse are clearly distinguishable, ctenophores also have symmetrical and reciprocal synapses where both sides have a presynaptic triad either facing each other or following one another (Hernandez-Nicaise, 1991). Reciprocal synapses are also present in bilaterians (Anderson & Grünert, 1988) while bidirectional symmetric synapses bearing vesicles on both sides are common in cnidarian jellyfish (Anderson, 1985).

The physiology of ctenophore neurons has not been studied experimentally therefore it can be only assumed based on the morphological and transcriptomic data as well effects of neurotransmitters on behavior or tissue preparations. The clear vesicles detected by electron microscopy in synapses and throughout mesogleal neurons are probably filled with low molecular weight neurotransmitters (Schwartz, 2002). However, it appears that serotonin, acetylcholine, dopamine, noradrenaline, adrenaline, octopamine, and histamine are not involved in neurotransmission in ctenophores (Moroz et al., 2014). Probably, L-glutamate acts as a neuromuscular transmitter as it can induce action potentials and contractions in muscles (Moroz et al., 2014) and several putative ionotropic glutamate receptors (iGluR) from Epsilon subfamily are expressed in ctenophore muscles (Alberstein et al., 2015; Ramos-Vicente et al., 2021; Sebé-Pedrós et al., 2018). Glycine can activate some of the Epsilon iGluRs present in muscles and neurons too (Alberstein et al., 2015; Sebé-Pedrós et al., 2018). SNN expresses a glutamate receptor (Alberstein et al., 2015; Sachkova et al., 2021) suggesting that it potentially might receive glutamatergic signals from sensory or mesogleal neurons bearing clear vesicles. Neurons of ctenophore SNN and many sensory cells are peptidergic (Hayakawa et al., 2022; Sachkova et al., 2021). Peptidergic dark vesicles are not localized to synapses but distributed throughout the SNN neuron body and neurites therefore they are probably released extrasynaptically and reach their targets by diffusion through mesoglea (known as volume transmission or "chemical wiring" observed in other animals too; Jékely, 2021). Interestingly, ctenophore neuropeptides do not share any detectable sequence similarity with other animals (Hayakawa et al., 2022; Sachkova et al., 2021). The only exception is nesfatin and phoenixin homologs, which are conserved throughout the animal kingdom and even in unicellular choanoflagellates (Yanez-Guerra et al., 2022); however, we still do not know if in ctenophores they are produced by nervous system and have a regulatory function. Despite the absence of sequence similarity, the overall neuropeptide precursor structure is conserved in ctenophores: long precursors include one or several mature peptides separated by cleavage sites (Hayakawa et al., 2022; Sachkova et al., 2021) suggesting that neuropeptide processing is similar to other animals. It appears though that negatively charged cleavage sites are much more frequently used by ctenophores and cnidarians compared to bilaterians that preferably use positively charged sites (Hayakawa et al., 2022). While ctenophores have hundreds of G protein-coupled receptors (GPCRs) and multiple degenerin/epithelial sodium channels reported to act as neuropeptide receptors in other animals (Moroz et al., 2014), ctenophore neuropeptide receptors have not been identified experimentally. A machine-learning method however predicted 122 pairs between 11 neuropeptides and 38 GPCRs (Hayakawa et al., 2022). Behavioral experiments showed that neuropeptides might be involved in the regulation of

swimming and feeding (Hayakawa et al., 2022; Sachkova et al., 2021). Neurotransmitter vesicles are probably released from ctenophore neurons using a conserved inventory of synaptic proteins (Burkhardt & Jékely, 2021), which is shared with other secretory cell types (Hayakawa et al., 2022). This sounds less surprising if we keep in mind that many proteins known as "synaptic" due to their role in bilaterian synapses are generally involved in exocytosis and even have evolved before the origin of animals (Burkhardt & Sprecher, 2017).

It is still unknown if the ctenophore nerve net is able to generate action potentials similar to their muscles (Hernandez-Nicaise et al., 1980) and combs (Moss & Tamm, 1987) however neurons are among the cell types with the highest expression of voltage-gated ion channel homologs (along with muscles, combs, and photocytes, Figure 1c) (Sachkova et al., 2021; Sebé-Pedrós et al., 2018). Potassium channels (Kv), the most abundant type of voltage-gated channels expressed in ctenophore neurons (e.g., SNN neurons express 35 Kv genes; Sachkova et al., 2021), belong to both Shaker and ctenophore-specific clades (Li et al., 2015). Interestingly, ctenophore-specific Kv genes are more represented in the neurons compared to Shaker, both in terms of total expression level and number of genes detected (Li et al., 2015; Sebé-Pedrós et al., 2018) suggesting that Kv genes originating after the split of ctenophores from the rest of animals significantly contribute to the unusual physiology of their neurons. Such a high number of voltage-gated ion channels coexpressed in a neuronal cell type is common for bilaterian nervous systems too and probably makes them more resilient (Goaillard & Marder, 2021). Even though two homologs of voltage-gated sodium channels are present in ctenophore neurons as well (Feuda et al., 2017; Sachkova et al., 2021), their specificity has not been characterized and potentially they may conduct calcium currents (Senatore et al., 2016). Voltage-gated calcium channel type 2 (Cav2; Moran & Zakon, 2014) is expressed in ctenophore neurons (Sachkova et al., 2021) suggesting that it might be involved in neurotransmitter release. While innexins are enriched in ctenophore neurons (Sachkova et al., 2021; Sebé-Pedrós et al., 2018), gap junctions and electric synapses have not been identified in their nervous system (Burkhardt et al., 2023).

Homologs of some major neuronal transcription factors such as bHLHA, SOX 1(B), and PRD-class homeobox are expressed by peptidergic neurons and sensory cells (Hayakawa et al., 2022; Sebé-Pedrós et al., 2018). Moreover, one of the paralogs of RNA-binding protein Elav critical for neuronal differentiation in bilaterians (Hilgers, 2023) is enriched in the SNN neurons (C33 cluster) (Hayakawa et al., 2022; Sebé-Pedrós et al., 2018). However, many "neuronal" transcription factors are not specifically enriched in neurons and shared with other cell types (Hayakawa et al., 2022), which is observed in bilaterian humans as well (Moroz & Kohn, 2015).

2 | THE DEBATE OF THE NERVOUS SYSTEM ORIGIN AND WHY IT IS CHALLENGING TO SOLVE

The question about the evolutionary origin of the nervous system and if it happened only once or multiple times has been widely debated. This debate started when molecular phylogenetics suggested that neuron-bearing ctenophores and not sponges might be the first lineage to branch off the animal tree (Figure 2a) (Dunn et al., 2008; Moroz et al., 2014; Ryan et al., 2013). Since nervous system is absent in sponges

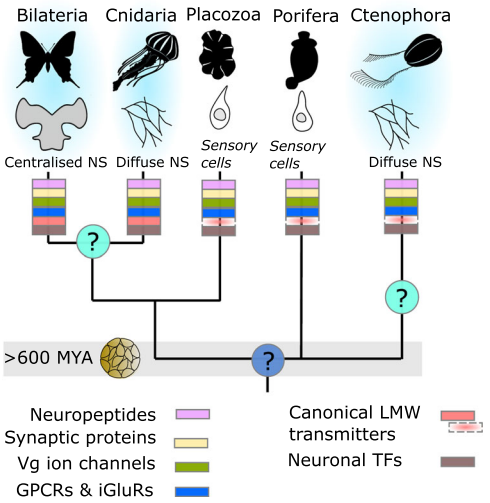

FIGURE 2 Phylogeny of the animal kingdom and the debate around the origin of nervous system. Animals with nervous systems (NS) are on a blue background. The two alternative scenarios that have been debated in the literature are shown by question marks in blue (single origin in the LCAA) or green (independent origins) circles. Genes encoding for the main building blocks of neurons can be found in all the animal lineages (shown by colored squares) (Burkhardt & Sprecher, 2017; Goaillard & Marder, 2021; Yanez-Guerra et al., 2022; Moroz & Kohn, 2015; Moroz et al., 2022). The LCAA (shown as a clump of cells) probably had a very simple morphology and potentially no identifiable neurons (Liebeskind et al., 2016). Animal icons were downloaded from Phylopic.org. GPCR, G protein-coupled receptor; iGluR, ionotropic glutamate receptor; LCAA, last common ancestor of animals; LMW, low molecular weight; MYA, million years ago; TFs, transcription factors; Vg, voltage-gated.

and placozoans, that would imply that either it independently evolved twice in Ctenophora and Cnidaria+Bilateria, or only once in the last common ancestor of animals and consequently lost in sponges and placozoans. While the phylogenetic dispute around the base of animal tree is still ongoing with several recent studies supporting either ctenophore-sister (Laumer et al., 2019; Ryan et al., 2013; Schultz et al., 2023) or sponge-sister (Feuda et al., 2017; Giacomelli et al., 2022; Kapli & Telford, 2020) hypothesis, it appears that the question about the origin of nervous system is not limited to solving the animal phylogeny. Regardless of the exact branching order of Ctenophora and Porifera, there are several possible scenarios of nervous system evolution: *homology* (shared origin in the last common ancestor of animals (LCAA) followed by divergence in Ctenophora, Cnidaria and Bilateria, and loss in Placozoa and possibly Porifera, depending on the animal tree topology) (Ryan & Chiodin, 2015); *convergence* (no neurons in the LCAA, origin of neurons separately in Ctenophora and Cnidaria+Bilateria lineages, possibly from different ancestral cell types); *parallelism* (separate origin of neurons in Ctenophora and Cnidaria +Bilateria from the same ancestral cell type in the LCAA (Jákely et al., 2015). It is worth to note that while convergence and parallelism are historically different terms meaning evolution of similar traits either from different or same ancestral traits (Belahbib et al., 2018), the boundary between them has blurred (Arendt & Reznick, 2008), and in the literature discussing the evolution of nervous system in ctenophores they have been used as synonyms (Moroz & Kohn, 2016; Moroz, 2015). While homology of all nervous systems might seem more probable and it might be difficult to accept that such a complex system as nervous could have evolved multiple times, we should keep in mind that convergence is a widespread phenomenon (e.g., complex multicellular organisms independently evolved several times in lineages of plants, fungi, and animals). Moreover, convergence occurs in nervous system too both at the whole system level (e.g., complex brains and longitudinal nerve cords probably evolved independently in different groups of bilaterians (Martín-Durán & Hejnol, 2021) and molecular level (e.g., connexins and innexins [Zakon, 2002], selectivity of sodium channels [Gur Barzilai et al., 2012]). One more possible option would be a "hybrid" scenario combining two or three scenarios described above. In fact, it has been pointed out that peptidergic sensory cells located around the ctenophore mouth might be homologous to bilaterian neurons (Burkhardt & Jékely, 2021), while the syncytial SNN might be a result of convergent or parallel evolution (Burkhardt et al., 2023).

Solving the problem of the nervous system origin turned out to be very challenging, mainly due to the complexity of the neuronal cell type, the hierarchical nature of homology between complex traits (Liebeskind et al., 2016), and the large evolutionary distances between the extant members of the main five animal taxa. Many of the key neuronal building blocks (e.g., synaptic proteins and voltage-gated ion channels, Figure 2) evolved before the origin of animals and are present in both unicellular relatives of animals and neuron-less sponges and placozoans (Burkhardt & Sprecher, 2017; Goaillard & Marder, 2021; Moroz & Kohn, 2015; Moroz et al., 2022; Yanez-Guerra et al., 2022) making it unclear what are the minimum requirements to build a neuron. Genes encoding these building blocks may have evolved at different times and undergone different evolutionary processes (Moroz & Kohn, 2016) making it difficult to conclude about the evolutionary history of a neuron as a whole (i.e., neuron is a complex trait). Ctenophore neurons retain some proteins that were present in the LCAA which however were lost in the well-characterized bilaterian lineages (e.g., Epsilon iGluRs, RIM II, and TMEM16L were lost in vertebrates and insects but expressed by ctenophore neurons (Piekut et al., 2020; Ramos-Vicente et al., 2021; Yuan et al., 2022). That can be interpreted either as an argument in favor of homology followed by divergence (if these proteins were expressed in the single neuronal precursor in LCAA) or convergence (if these proteins were expressed in LCAA cell type that was lost in vertebrates and insects but gave rise to ctenophore neurons). Ctenophore genome contains multiple unique genes with no detectable similarity to characterized proteins (Moroz et al., 2014), and therefore around quarter of genes expressed in the SNN are likely ctenophore innovations with unknown function (Sebé-Pedrós et al., 2018) contributing to the unique neuronal phenotype. These unique genes may be interpreted either as a reason behind the highly divergent neuronal phenotype or as key players in the independent evolution of ctenophore neurons.

One of the obstacles in molecular characterization of ctenophore neurons was the fact that many of the typical neuronal markers known from bilaterians were not specifically enriched in neurons but shared with other cell types (Hayakawa et al., 2022; Sebé-Pedrós et al., 2018). Potentially, that may be explained by co-option of neuronal proteins in other new ctenophore-specific cell types, for example, in colloblasts sharing a developmental progenitor with neurons (Babonis, 2018), as well as expressing homologs of proteins involved in synaptic function, vesicle transport and release, and

neuropeptide processing (Hayakawa et al., 2022). Moreover, evolution of other cell types may have affected the evolution of ctenophore neurons and even contributed some novelties due to potentially shared regulatory elements (Liang et al., 2018).

Another consideration is whether it is always possible to prove homology between cell types at such long evolutionary distance. For example, epithelium had been considered conserved throughout animals and key for the evolution of metazoans (Tyler, 2003). However, recent studies challenged this notion by revealing that ctenophores that are equipped with epithelium are lacking some proteins key for the organization of epithelium in bilaterians while sponges have a more complete epithelial toolkit but mostly lack a "true" epithelium (Belahbib et al., 2018).

Regardless of the exact evolutionary mechanism, a consensus that first neurons had no synapses and evolved from some kind of secretory cells (possibly different types) has recently emerged (Burkhardt & Jékely, 2021; Colgren & Burkhardt, 2022; Hayakawa et al., 2022; Jékely, 2021; Moroz, 2021). The first neurotransmitters were either peptides (Hayakawa et al., 2022; Jékely, 2021) or both low molecular weight compounds and peptides (Moroz, 2021). Thus, even if all neurons share a common evolutionary origin, it might be at the level of a secretory cell type in the morphologically simple last common ancestor of animals (Jékely, 2021; Liebeskind et al., 2016; Moroz, 2021) (so-called deep homology).

3 | CONCLUSION

As a wider range of modern techniques has recently become available in ctenophores (e.g., single-cell RNAseq [Sebé-Pedrós et al., 2018] and connectomics [Burkhardt et al., 2023]) and ctenophore species have progressed towards becoming established lab models (e.g., culturing and CRISPR/Cas9 knock-outs have been reported [Presnell et al., 2022; Soto-Àngel et al., 2022]), new critical insights into the biology of their neurons have been revealed. Earlier studies have established such key approaches as electrophysiology and calcium imaging in ctenophores; however, it has been achieved only in comb plates (Moss & Tamm, 1987; Tamm & Terasaki, 1994) and muscles (Moroz et al., 2014; Ortiz et al., 2023), while direct measurements of neuronal activity have not been reported. Thus, more experimental approaches are urgently required to understand the function of ctenophore neurons. For example, electrophysiology and calcium imaging directly on ctenophore neurons are required to understand how neuronal impulses are transmitted in their nervous system. Biochemical characterization and genetic knock-ins are necessary to reveal the function of multiple unique ctenophore proteins. This new knowledge will shed light on the molecular mechanisms employed in ctenophore nervous system and will enable further evolutionary comparisons with nervous systems of cnidarians and bilaterians as well as neuron-less sponges and placozoans.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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