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Rapid Conduction and the Evolution of Giant Axons and Myelinated Fibers

Review

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Nervous systems have evolved two basic mechanisms for increasing the conduction speed of the electrical impulse. The first is through axon gigantism: using axons several times larger in diameter than the norm for other large axons, as for example in the well-known case of the squid giant axon. The second is through encasing axons in helical or concentrically wrapped multilamellar sheets of insulating plasma membrane — the myelin sheath. Each mechanism, alone or in combination, is employed in nervous systems of many taxa, both vertebrate and invertebrate. Myelin is a unique way to increase conduction speeds along axons of relatively small caliber. It seems to have arisen independently in evolution several times in vertebrates, annelids and crustacea. Myelinated nerves, regardless of their source, have in common a multilamellar membrane wrapping, and long myelinated segments interspersed with 'nodal' loci where the myelin terminates and the nerve impulse propagates along the axon by 'saltatory' conduction. For all of the differences in detail among the morphologies and biochemistries of the sheath in the different myelinated animal classes, the function is remarkably universal.

Introduction

The rapid conduction of nerve impulses would be an obvious priority for the nervous systems of animals constantly challenged with life-or-death decisions, and one might expect to see a trend towards increasing conduction speed over the course of evolution. As animals developed more sophisticated behaviors, and as they were pressed to invade riskier environments — such as those outside of their protective shells or burrows, or in the water column away from sources of cover — mechanisms for rapid conduction must have become a distinct advantage. Nerve fibers that conducted more rapidly enhanced the timeliness of escape responses and may have enhanced predatory-capture capabilities and other neural-processing functions [1].

What factors determine the speed of impulse conduction? Many nerve-fiber parameters do and are potentially under evolutionary selective pressure [2]. Two are especially critical: the axial (longitudinal) resistance of the fiber to electrical current (r_i and r_o in Figure 1A), and the capacitance of axon surface that must be charged to threshold to regenerate a nerve impulse farther down the axon. To illustrate this, consider the case of a non-myelinated axon as represented by the equivalent electrical circuit in Figure 1A. Current entering through open sodium channels (1) flows longitudinally along the axon interior to charge the capacitance of adjacent resting membrane (2). The speed of charging depends on the capacitance of the membrane (c_m in Figure 1A) and the longitudinal resistance ($r_i + r_o$). The faster the charging — the smaller the product $(r_o + r_i)c_m$ — the sooner the non-excited region reaches impulse threshold, and the faster the impulse travels. Conduction speed can thus be increased quite effectively either by decreasing the interior resistance (r_i) or by decreasing the trans-fiber capacitance, or both. In this review, we shall examine the two major mechanisms that have evolved to increase nerve-impulse conduction speed, and describe how their employment fits into the phylogenetic scheme of the animal kingdom.

The Easy Solution: Axonal Gigantism

Let us first consider strategies for decreasing the interior resistance, r_i. Increasing the interior diameter of the fiber is an easy way to do so, as resistance drops as the square of diameter. This increases conduction speed in proportion to the square root of the interior diameter [3]. This strategy for speeding impulses leads to gigantism of axons in time-critical neural circuits. Such axons may be several times larger than other large axons in that organism. Giant axons are found in circuits throughout most of the more advanced bilateria, including those mediating rapid withdrawal of tube worms, escape jetting of squid, tail flip responses of lobsters and crayfish, startle reactions of insects and 'C'-start escapes of fish [4].

While no satisfactorily comprehensive study has been made of the size of giant axons in relation to selective pressures (for example, the susceptibility of an organism to sudden predatory attack), it has been qualitatively observed that axonal gigantism appears more pronounced in more 'active' taxa than in more sedentary or protected ones [5]. Contrary to common belief, giant axons are employed even in organisms so small that the time-difference advantage they confer would seem inconsequential, such as fruit flies and copepods [6]. However, smaller organisms, living on shorter length and time scales than larger ones, gain similar relative benefits from temporal savings. The 'easy solution' works for organisms large and small, but it takes space.

The Second Solution: Myelin

The alternative solution to producing rapid conduction is to decrease the transverse capacitance between the inside and outside of a nerve fiber. In all recognized cases where this route has been taken, it is achieved through the development of a myelin sheath, a lipid-rich multilamellar membrane coating

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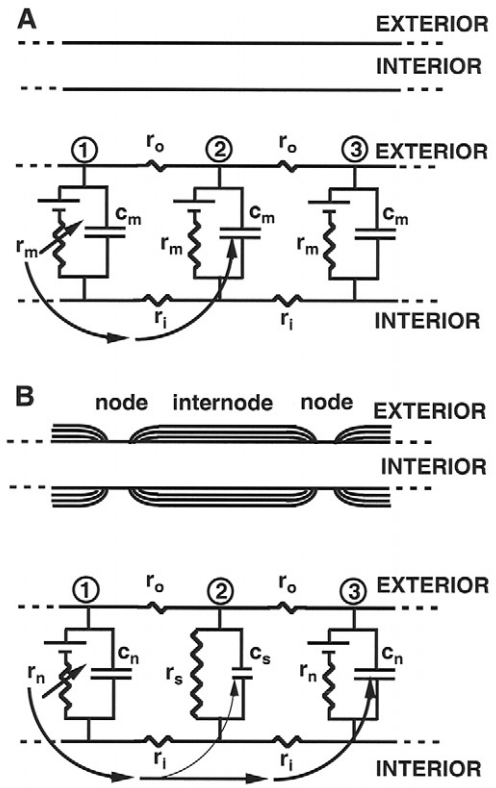

Figure 1. Comparison of nerve impulse current flow in electrical circuit analogs of unmyelinated (A) and myelinated (B) nerve fibers.

(A) Sodium ions entering an unmyelinated fiber through voltage-gated channels in an active region (1) generate current that flows onto the capacitance of immediately adjacent membrane (2), charging it to a level where its sodium channels open and it starts to conduct current, whence the sequence repeats. (B) In myelinated fibers, however, the entering sodium current (1) charges adjacent inexcitable regions covered by myelin much more rapidly (2) and at the cost of many fewer ions, hence the current is available to flow without delay to the next node (3) to initiate an impulse there. Longitudinal resistance along the fiber is composed of inside (r_i) and outside (r_o) components, the latter usually being small enough to be ignored.

of axons (Figure 2). All significant structural characteristics of this sheath are held in common by every myelinated fiber in vertebrates, from sharks to humans [7]. These include a tight investment of the axon by helically wound glial membrane, punctuated at intervals by gaps in the sheath completely encircling the axons, the 'nodes of Ranvier'.

How these features speed impulses is shown diagrammatically in Figure 1B. With an impulse occurring at an exposed node (1), insulation by the non-conductive lipid sheath increases the transverse resistance (r_s) and, more importantly, reduces the transverse capacitance (c_s) of immediately adjacent internodal membrane (2). This, in turn, reduces currents flowing through internodal surfaces, and speeds internode charging. Current from the active node is thus less attenuated over distance, and hence more is available sooner for charging membrane at distant nodes (3).

The restriction of exposed membrane at nodes also reduces the area of membrane into which this current must flow, and hence reduces its capacitance as well. This increases its rate of charging — technically, the time-constant for charging nodal capacitance, $2r_i\ c_n$, is reduced by reducing c_n — allowing the threshold to be reached more quickly and thus speeding the impulse even more. Furthermore, the number of layers in the myelin sheath increases proportionately to interior ('axonal') diameter. Thus, the internodal capacitance per unit area of surface decreases with fiber diameter, adding to the effects from diameter-dependent axial resistance, giving the conduction speed a first power (rather than square root) dependence on diameter over a substantial range [2].

The Distribution of Myelin in the Animal Kingdom

Myelin is absent in primitive members of the vertebrate line (hagfish and lampreys) [8]. The first myelinated vertebrate was likely to have been a placoderm [9], the antecedent of contemporary sharks and bony fish. From the early days of microscopy of the nervous system, myelin sheaths have been described in both vertebrates and invertebrates [10–14]. With the advent of electron microscopy focused primarily on vertebrate material [15], myelin has generally been viewed as an exclusively vertebrate innovation. However, electron microscopy also reveals that many of the myelin sheaths described in invertebrates in fact have similar structure and apparently identical function (Figure 3).

As in other cases of convergent evolution, such as eyes and wings, the detailed implementation varies, but sheaths that restrict current escape between nodes and reduce impulse-sustaining nodal membrane are found in crustaceans (malacostraca, including decapod shrimp and copepoda) and annelids (polychaetes and oligochaetes). Myelin has not been reported in

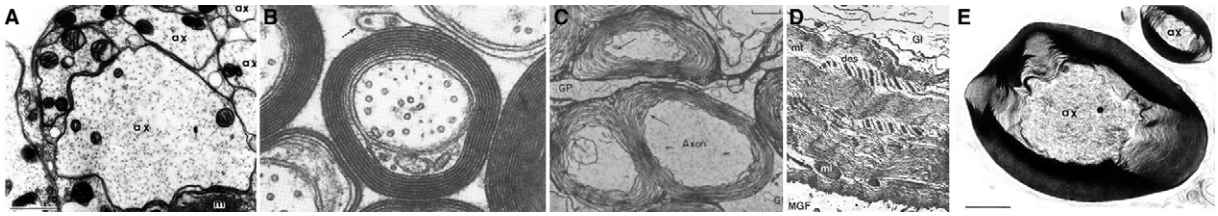

Figure 2. Different forms of speed-enhancement in different taxa.

(A) Unmyelinated giant sensory axon from a copepod first antenna (*Candacia*; photo courtesy of April Davis). (B) Myelinated axons from a dog. (C) Myelinated axons from a prawn (*Macrobrachium*). (D) Portion of a myelin sheath from an earthworm (*Lumbricus*). (E) Myelinated copepod axons (*Euchaeta rimana*). (Panels reproduced with permission from: (B), [25]; (C), [22]; (D), [19]; (E), [17].)

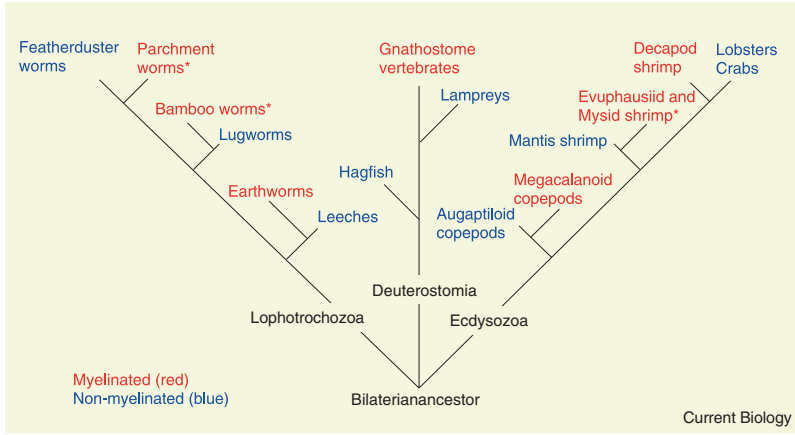

Figure 3. Simplified phylogeny of bilateria showing taxa reported to possess myelin (red) and related non-myelinated taxa (blue).

Taxa marked by an asterisk have not had myelination status confirmed by electron microscopy.

either molluscs or insects. In these and other non-myelinated taxa, such as crabs and lobsters, elaborate investments of nerve fibers by glial and connective tissue sheaths are often found which do not, however, appear to have either the insulative properties nor the distinctive fine structure of myelin [16].

It is difficult to pinpoint the ecological conditions and selective pressures that gave rise to the evolution of myelin. Among crustaceans, a pelagic lifestyle involving exposure to visual predators in the open ocean appears to have been one factor. Benthic decapods (crabs and lobsters) lack myelin. Most large non-myelinated copepods of the open ocean inhabit dimly lit depths by day and only migrate toward the surface to feed at night [17]. As is the case with axonal gigantism, myelination is found even in very small organisms. Studies are needed of myelination patterns and ecology for annelids and for a broader selection of crustaceans.

Myelin Blocks Internodal Current Leakage

Several variants in myelin structure all achieve the same functional results (Figure 4). In all known organisms, the insulating sheath that reduces electrical capacitance, and increases resistance, between the interior and the exterior of a nerve fiber is achieved through multiple layers of lipid membrane. Such a sheath must still make provisions for blocking the current leakage that would short circuit its insulating properties, and different solutions are appropriate for the internode and node.

In annelids, as with vertebrate myelin, the membrane appears to be spirally wrapped [18]. By thin section electron microscopy, a continuous sheet of glial cell membrane is observed that starts at the axon and spirals outward (Figure 4A). To prevent short-circuiting by current following along the spiral path between lamellae, membrane ‘compaction’ has evolved, in which electrically conductive cytoplasmic and extracytoplasmic spaces are minimized by the near-fusion of apposed internal and external leaflets of the lipid bilayer. In the vertebrates, this leads to the characteristic lamellar structure of alternating major dense lines and intraperiod lines corresponding to the close apposition of cytoplasmic and external lipid leaflets of the myelinating glial cell. Myelin of the earthworm (*Lumbricus*) consists of 60 to 200 such layers, often, but not always, compacted, with most of the cytoplasm eliminated (Figure 2D). A combination of compaction and specialized inter-laminar attachment zones resembling desmosomes of epithelia appear to provide the necessary blockage of transverse leakage current through the internode. The conduction speed of earthworm myelinated fibers is a few fold higher than that of non-myelinated fibers of the same diameter [19].

All malacostracan (shrimp) myelin described in detail so far has been seen to be concentrically arranged: lamellae of a given layer encircle the central axon, abutting corresponding margins of the same layer in specializations termed ‘seams’ [20]. To ensure the integrity of transverse electrical insulation, concentric wraps require only that tight seals be made at the

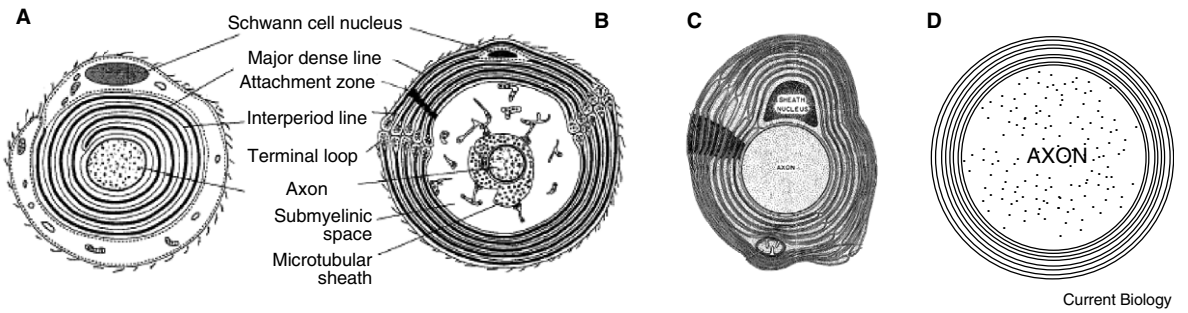

Figure 4. Schematics of myelin wraps in the different myelinated taxa.

(A) Vertebrate; (B) penaeid shrimp; (C) palaemonid shrimp; (D) copepod. (Panels reproduced with permissions from: (A,B), [20]; (C), [22].)

seams, and hence the premium on compactness is not so great. Shrimp myelin is sometimes compact and sometimes only semicompact (Figure 2C; Figure 4B,C), that is, it excludes only the extracellular gap while retaining some cytoplasm. What is important is that the conductive spaces between the layers be isolated from each other by a continuous membranous barrier or by tightly joined appositions at the seams. This fact is sometimes overlooked, leading some to conclude incorrectly that invertebrates lack 'true' myelin.

The fibers of penaeid shrimps are unusual in that the axon occupies only a part of the space within the sheath. The rest is occupied by glial cytoplasm or a large extracellular space termed the 'submyelinic space' (Figure 4B). Current entering the axon through voltage-gated channels flows readily out of it again, as in non-myelinated nerves, but it is trapped and confined in the submyelinic space, as if it were a giant axon filling the space. Penaeid fibers of 120 mm diameter conduct impulses at the fastest speeds known: over 200 m s^{-1}, compared with ~100 m s^{-1} for the fastest recorded myelinated vertebrate axons [21].

Copepod myelin, too, is concentrically organized. It is compact in the outermost layers of the sheath, but often there is a substantial gap between rings (Figure 2E; Figure 4D). There is no evidence of seams, so there appear to be no weak spots in the sheath through which current might pass more easily than through the membrane itself. Perhaps this is why only cytoplasmic space is consistently eliminated in most regions of copepod myelin.

Nodal Gaps Sustain Impulses

Small gaps in the sheath at intervals along the fiber, through which ionic current can flow between outside and inside, are needed to support nerve impulses. In vertebrates and palaemonid shrimps, the requisite breaks in the sheath occur at circumferential 'nodes of Ranvier', in which the gap extends completely around a nerve fiber [12,22,23]. In oligochaetes, penaeid shrimps and copepods, on the other hand, nodes are 'focal', being restricted to small openings in the sheath rather than breaks that encircle the fibers [19,20,24]. This variation in form is not, however, greatly significant for the basic function, which is to admit current to sustain nerve impulses. In penaeids, for example, these nodes are the sources and sinks for current just as are the circumferential nodes of vertebrates [20].

Blocking Current Leak at Lamellar Margins

The short-circuit problem is also acute at the margins where layers of myelin terminate, which offer an opportunity for current to insinuate itself between laminae. In vertebrates, this is prevented by specialized paranodal attachment regions ('septate junctions') between myelin and axon that block access [23,25]. While there are no septate junctions between glia and axon at earthworm nodes, the glial layers surrounding a node are tightly apposed to the axon and heavily populated with desmosome-like specializations [19] which presumably contribute to the structural and/or electrical integrity of the myelin at the nodes. The glial margins in contact with the axon in the paranodal region of *Palaemonetes* exhibit the septate structures reminiscent of those in the same regions of vertebrate nodes [22]. At copepod nodes, no distinct specializations between myelin lamellae and the axonal membrane have been observed. Instead, the myelin layers seem to fuse with axonal membrane in the paranodal region [24]. Again, the impression is of very tight control over current leakage between the myelin layers at a potential weak point. The important functional characteristics of myelin are thus shared by several taxa, albeit the precise form these take varies.

Adhesion Mechanisms in Vertebrate Myelin

It is likely that myelinating cells originated from generalized ensheathing cells that engage neurons even in unmyelinated organisms. The first myelinating cells may have resembled ensheathing cells that we find in extant species, such as satellite cells of the dorsal root ganglion [26]. In the vertebrate peripheral nervous system (PNS), just one Schwann cell myelinates a single axonal segment. By contrast, axons in the central nervous system (CNS) are myelinated by oligodendrocytes, and each oligodendrocyte can myelinate several axonal internodes. One might imagine that a reduction in oligodendrocyte cell body number, while maintaining the same number of myelinated segments, saved space within the vertebrate skull, which could then be devoted to a steadily increasing number of neurons over evolutionary time [27].

What molecular components have evolved to subserve these vital functions of myelin? By far the best-studied myelin is that of the vertebrates. As with other myelins, vertebrate myelin has a very complicated mature morphology, and studying its anatomy yields little information about how the sheath actually develops around an axon, a process that is still poorly understood. Peripheral nerve myelin in terrestrial vertebrates is organized into highly compact and non-compact regions. The compact zone is held together at both cytoplasmic and extracellular membrane surface appositions by a transmembrane protein, Protein Zero (P_0), a glycoprotein comprising a 124 amino acid extracellular domain, a single transmembrane segment, and a positively charged 69 amino acid intracellular domain [28]. The extracellular domain is similar in sequence to immunoglobulins, and so P_0 is a member of the immunoglobulin gene superfamily: in fact, its structure makes it one of the 'simplest' immunoglobulin-like membrane proteins.

The extracellular domain of P_0 functions homophilically, adhering to other P_0 molecules across the extracellular cleft. This has been demonstrated in experiments where P_0 has been expressed in non-adherent cell lines. Ultrastructural analysis of cells forced to adhere to one another as a result of P_0 expression shows that the cell–cell interfaces acquire a regular morphology highly suggestive of the extracellular intraperiod line of mature PNS myelin [29,30]. Because P_0 can confer homophilic adhesion in any cell in which it is expressed, it would seem to be a kind of universal adhesion molecule, and the mechanisms by which the extracellular domain of P_0 adheres to itself are general ones that clearly can operate even when removed from the context of the myelin sheath.

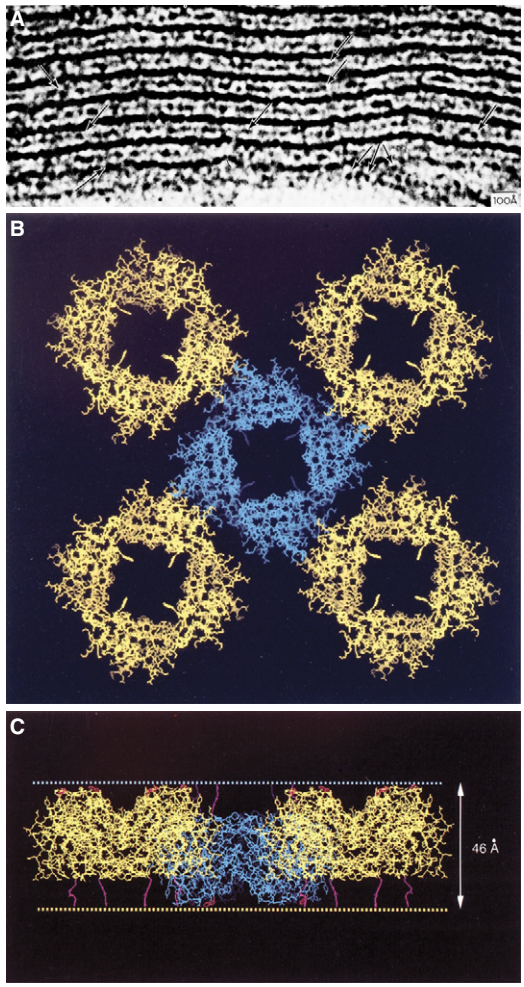

Figure 5. Protein Zero structure.

(A) Transmission EM of frog sciatic nerve showing regular globular structures (arrows, presumably P_0 tetramers) in the extracellular space (see [15]). (B) Orthogonal view of interlocking P_0 tetramers. Yellow and blue tetramers emanate from apposing lipid bilayers, and interlock in the extracellular space. (C) Homophilic interactions of tetrameric P_0 units as determined by X-ray crystallography; compare with (A). (Panels reproduced with permission from: (A), [15]; (B,C), [32].)

Early ultrastructural analysis of frog sciatic nerve by Fernandez-Moran [15,31] revealed a regular organization of electron-dense 'globules', interconnected with each other, apparently suspended in the extracellular milieu, and attached by electron dense 'tendrils' to the extracellular aspect of the myelin bilayer (Figure 5A). A half century after these images were published, Shapiro *et al.* [32] analyzed the crystal structure of the P_0 immunoglobulin domain and determined that P_0 exists as interconnecting tetramers arranged in a lattice suspended within the extracellular compartment (Figure 5B,C). The tetramers are anchored to each other through peptide backbone interactions, and they are further anchored to the apposing bilayer by way of tryptophan side chains embedded in the hydrophobic phase of the membrane (Figure 5C).

Although P_0 can mediate the adhesion of myelin membranes, leading to the appearance of the intraperiod and major dense lines by virtue of exposure of the molecule on both extracellular and cytoplasmic aspects, P_0 is not present in the CNS of mature terrestrial vertebrates [33]. A set of polypeptides termed 'proteolipid proteins' (PLPs) — DMa, DMb and DMg, DM20, M6a and M6b — have been identified which are abundant integral membrane proteins in the CNS, but their precise function in the generation of the myelin sheath is not yet understood [34,35]. Clearly though, P_0 and the PLPs are not functionally equivalent in myelin sheath biogenesis. The sequence relatedness of the proteolipid proteins to primitive channel proteins [34] may give us clues as to the function of these very hydrophobic proteins in the myelin sheath.

No homologues of P_0 or other non-tetraspan integral myelin proteins known from vertebrates have been found in invertebrates so far, although immunoreactivity to P_0 antibodies has been reported for a 50 kDa protein from shrimp myelinated nervous system [36]. However, genes for members of the proteolipid family have been reported both in protochordates and protostome invertebrates [37]. These suggest the possibility of common ancestry for at least some myelin components across the animal kingdom. Much remains to be learned about myelin proteins, their identities among invertebrates and their antecedents in both vertebrates and invertebrates.

Nodal Molecules

In recent years, there has been an explosion of interest in the node of Ranvier and the region immediately surrounding it in vertebrate nerve fibers [38,39]. This is because the node of Ranvier is now recognized as a metabolically highly active zone, and it is of course the site at which the voltage-gated sodium channels are highly concentrated (see above). Nodal and paranodal morphology is complex (Figure 6): sharply delineated microdomains are recognized both morphologically and biochemically within what amounts to just a few microns of length in either direction from the centre of the node of Ranvier (Figure 7) [40]. Ion channels, adhesive proteins, and proteins with as of yet unrecognized functions assemble at the node and in its vicinity, in very precise relationships to one another that we are just beginning to understand.

Ultrastructural studies show that the myelinating glial cell forms a heterotypic junction with the underlying axon, and this junction takes the form of periodic regularly arranged septa highly reminiscent of those observed between epithelia cells in *Hydra* and in the nerve–blood barrier of *Drosophila*. In *Drosophila*, neurexin IV is one hallmark protein of the nerve–blood barrier where the septa are found [41]. While no myelin is to be found in flies, in vertebrates virtually identical septa form the axoglial junction between the myelinating glial cell and underlying axon, and it is of great interest that the septa also contain a type IV neurexin-contactin-associated protein (Caspr), closely related in terms of evolution to its *Drosophila* counterpart [41–43]. Conservation of these proteins over 750 million years of evolution strongly suggests that they are of major importance in the generation of 'septal' bonds between cells, but their precise function in the generation of the septate morphology has yet to be determined.

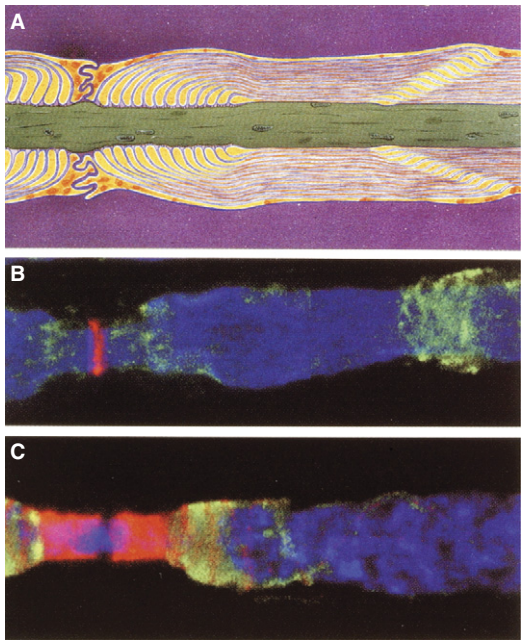

Figure 6. Molecular microdomains at the vertebrate node of Ranvier.

(A) Diagram of a longitudinal EM section showing paranodal loops terminating the myelin layers on the left, and a Schmidt-Lanterman incisure at the right. (B) Immunoreactivity for sodium channels (magenta) and myelin-associated glycoprotein (green). (C) Immunoreactivity for Caspr in the paranodal domain (magenta) and potassium channels (green). (Reproduced with permission from [39,40].)

Recent work has also shed light on a long-standing problem in myelin biology: what is the signal by which a glial cell recognizes an axon to be myelinated, as opposed to an axon that becomes merely ensheathed but no myelin is formed? A series of fascinating papers (see [43,44], and references therein) collectively reveal that axons to be myelinated express high levels of neuregulin-1 on the axonal surface that the myelinating cell recognizes as a positive signal for myelination to proceed.

Evolutionary Pressures

Myelin sheaths are frequently associated with rapid reactions, especially in invertebrate taxa. For fibers of a few microns or more in diameter, myelin speeds the conduction of nerve impulses by a factor of ten or more compared to unmyelinated fibers of the same diameter. This increases the nervous system's information processing capacity and delivery speeds, decreasing reaction times to stimuli, increasing temporal precision, more closely synchronizing spatially distributed targets (such as different regions of a muscle sheet), and providing for shorter delays in feedback loops (for example in muscle control). Because less current is needed to satisfy the charging needs of myelinated fibers, mean sodium channel densities averaged over the length of a fiber are much lower than for unmyelinated ones. This results in a smaller ionic imbalance that must be restored after an impulse passes and confers a several hundred-fold improvement in metabolic efficiency for recouping the energy cost of nerve impulse traffic. For a nervous system such as ours, which already accounts for 20% of the body's resting metabolic energy budget, this is not an inconsequential advantage. Another advantage is economy of space: to achieve the same ten-fold improvement on conduction speed through increasing axonal diameter, axons would have to be 100 times larger (with a comparable scale-up in soma size to accommodate the metabolic needs). Imagine yourself with a 100-fold thicker spinal cord!

Myelin in any group is a highly structured tissue, with many specialized molecules interacting in complex ways, and clearly with a long evolutionary history in each of the lines in which it has appeared. Given the phylogenetic separation among myelinated taxa, myelin may be presumed to have arisen independently in each of the major bilaterian lineages (Figure 3): the deuterostomes (gnathostomes), the lophotrochozoa (polychaetes and oligochaetes) and the ecdysozoa (copepods and malacostracans). So ancient is its evident appearance in each of these lines, and so sophisticated its morphological and chemical structure, that its exact origin in most of those lines is hard to establish. Even in vertebrates there is a great evolutionary distance between the unmyelinated hyperoartia (lampreys) and the gnathostomes.

The initial steps in the evolution of myelination may not, however, be that difficult to reconstruct. Electrically sealing together two apposed membrane surfaces over a small region of axon decreases its transverse capacitance and proportionately speeds impulse propagation along it. The sealing can be achieved by narrowing the conductive space, either cytoplasmic or extracytoplasmic, between adjacent axonal and/or glial membranes — as might have been achieved, for example, by an early version of

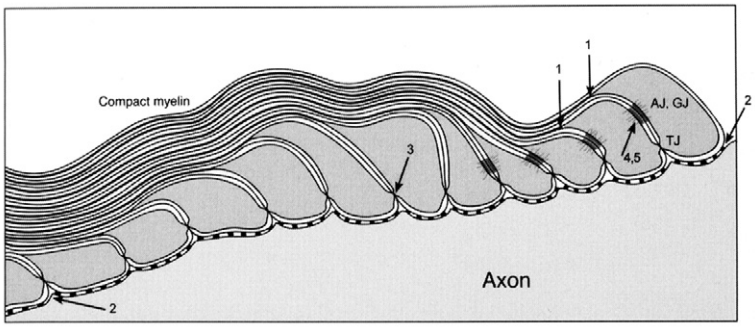

Figure 7. Diagram of paranodal loops at a vertebrate node of Ranvier.

Black dots between the loops and the axolemma indicate septate junctions. (Reproduced with permission from [39].)

a homophilic P_0 analog — or through impermeable specializations at margins, for example precursors of septate junctions. Even the random sealing of patches of single-layer glial membrane over half of an axon's surface is predicted to increase conduction speed by about 20%. Once such a process has started, it is not difficult to imagine a sequence of small improvements driven by natural selection that would ultimately lead to the complex structures we see today. This is speculative, however; no cases have been described so far of 'intermediate stages' in extant groups. Developmental sequences, the lack of fossil records and the paucity of candidate molecular precursors so far identified have made the task more difficult. Perhaps better insight will be gained through increased attention to myelin evolved in the invertebrates.

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