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Review

# Molecular regulators of nerve conduction — Lessons from inherited neuropathies and rodent genetic models

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ABSTRACT

Myelinated nerve fibers are highly compartmentalized. Helically wrapped lipoprotein membranes of myelin are integrated with subsets of proteins specifically in each compartment to shape the physiological behavior of these nerve fibers. With the advance of molecular biology and genetics, many functions of these proteins have been revealed over the past decade. In this review, we will first discuss how action potential propagation has been understood by classical electrophysiological studies. In particular, the discussion will be concentrated on how the geometric dimensions of myelinated nerve fibers (such as internodal length and myelin thickness) may affect nerve conduction velocity. This discussion will then extend into how specific myelin proteins may shape these geometric parameters, thereby regulating action potential propagation. For instance, periaxin may specifically affect the internodal length, but not other parameters. In contrast, neuregulin-1 may affect myelin thickness, but not axon diameter or internodal length. Finally, we will discuss how these basic neurobiological observations can be applied to inherited peripheral nerve diseases.





**Contents**



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## Introduction

Nerve conduction study (NCS) has been one of the most important tools in diagnosing peripheral nerve diseases. Compound action potentials (CAPs) are evoked by electrical stimuli delivered to both distal and proximal sites of peripheral nerves. If the recording is made on muscles, the response is called compound muscle action potential (CMAP). Several measurements can be collected from CAP, including amplitudes of the potential and speed of the CAP propagation in different nerve segments (such as distal latency in distal nerve, conduction velocity in middle nerve segment, or F-wave latency in entire loop of peripheral nerve). Alterations in these measurements have been classified into two categories: de-/dysmyelination versus axonal loss. NCS in de-/dysmyelination shows slowed conduction velocity with prolonged distal latency and F-wave latency. Demyelination denotes a rupture or removal of fully differentiated Schwann cell membrane laminae that ensheath the axons. Dysmyelination is used for neuropathies with abnormal development of myelin, which is typically seen in patients with inherited neuropathies (such as Charcot–Marie–Tooth diseases, abbreviated as CMT). In contrast, axonal neuropathies demonstrate a decrease of CAP/CMAP amplitude with normal or minimally slowed conduction speed (Kimura, 1993).

Over many decades, studies through NCS have been descriptive, notwithstanding their clinical use. However, this nature starts to change with the advance of molecular genetics. In this review, we will discuss how human genetic mutations and rodent models may deepen or even revise our interpretation of NCS. A multi-discipline approach may soon reveal the molecular basis of NCS findings. We will discuss how these important discoveries may be translated into clinical practice.

### *Myelinated nerve fibers are highly compartmentalized by their unique protein architecture*

Axons are either circumscribed by a single-layered Schwann cell membrane to form non-myelinated nerve fibers or wrapped by many layers of Schwann cell membranes to produce myelinated nerve fibers (Fig. 1A). One Schwann cell invests many non-myelinated axons, but the relationship between a Schwann cell and a myelinated axon is always one to one. Nerve fibers are bundled by perineurium into multiple fascicles before finally being encased by epineurium to form the whole peripheral nerve. Peri-/epineurium is formed by many peri-/epineurial cells along with collagen fibers, microvasculatures, and fibroblasts. Peri-/epineurial cells are connected by tight junctions and adherens junctions to seal the space between these cells, thereby protecting nerve fibers from being accessed by external pathogens (Peltonen et al., 2013).

Unlike the uniform “cable” of non-myelinated nerve fibers, myelinated nerve fibers are highly compartmentalized. Each Schwann cell wraps around an axon to form a segment of compact myelin that defines the territory of an internode. This wrapping is interrupted by a punctate gap, called the node of Ranvier. The node is demarcated by two paranodes on each side where Schwann cell membranes attach axolemma via a protein complex, called septate-like junctions. Immediately adjacent to the axoglial, septate-like junction, the portion of the myelin plus its interacting axolemma is called the juxtaparanode. Each compartment contains a unique set of protein constituents (Fig. 1B). For instance, at the node of Ranvier, voltage-gated sodium channels ($Na_v$) are concentrated. $Na_v$ interacts with neurofascin-186 and gliomedin through ankryn-G and βIV-spectrin. The paranodal region contains the Schwann cell proteins myelin-associated glycoprotein (MAG), Connexin-32 (Cx32), and

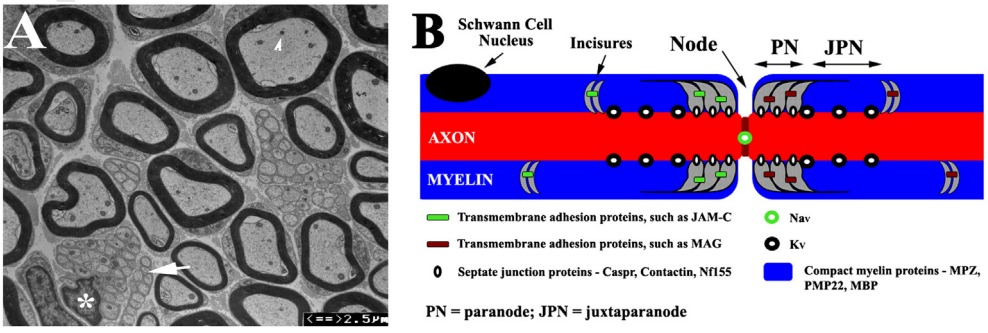


**Fig. 1.** (A). Transverse section of a 3-month-old mouse sciatic nerve was examined by electron microscopy. Myelinated nerve fibers showed different diameters, which varied positively with myelin thickness. Intra-axonal organelles, such as mitochondria, were visible (arrowhead). Between myelinated nerve fibers, there were Remark bundles (arrow) where a Schwann cell (its nucleus marked by an asterisk) invests a group of non-myelinated nerve fibers. (B). A diagram illustrates the localizations of proteins on myelinated nerve fibers. Specific subsets of proteins reside in different compartments (node, paranode, juxtaparanode and compact myelin of internode) of the myelinated nerve fiber.

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