Public Abstract
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Title:DETERMINING THE MECHANISM OF NF C-TERMINAL MEDIATED RADIAL GROWTH OF MYELINATED AXONS

Speed is important to the nervous system. It must respond to external stimuli within a reasonable time frame. In an effort to understand the development of the peripheral nervous system we study proteins that are specific to mature nerve cells or neurons. In response to external stimuli neurons of the peripheral nervous system communicate with muscles through electrical signals or messages called action potential. Myelination is a key feature of mature peripheral neurons. This process involves the formation of myelin (an electrical insulating material) around axons (part of the nerve cell that conduct electrical signals) to create an insulating layer. Consequently, nerve impulses or electrical signals are conducted faster in myelinated nerve cells. Signals originating from myelin result in a large increase in axonal diameter. It is suggested that the target for these signals is neurofilaments, a group of proteins that are found in large myelinated axons and are essential for diameter growth. The protein group is composed of subunits classified as, light, medium and heavy. The absence of neurofilaments results in axons with small diameter and slowed conduction velocities. The mechanism for an axon's diameter growth has long been argued. Previous evidence has pointed to myelin-dependent modification of regions of neurofilaments that are located within the medium and heavy subunits. Utilizing gene-targeting strategies to generate various mouse models the role of neurofilaments in diameter growth was determined. In previous studies a region of neurofilament medium was identified as being required for diameter growth and optimal nerve conduction velocity. In a more recent study it was determined that increasing the length of this region increased diameter growth. Moreover, the neurofilament medium subunit was genetically altered such that it could no longer be modified in response to myelination. Surprisingly, prevention of what was considered an extremely important modification did not affect axonal diameter. Taken together, these results suggest that a region of neurofilament medium subunit regulates the diameter of the axon, but it does so in a manner that is independent of myelin-dependent modification. These studies were done primarily in motor neurons. Therefore, I extended analysis to sensory neurons. Our results suggest that increased axonal diameter in sensory neurons was selected for through a mechanism that was different from motor axons and was independent of myelin-dependent modification of neurofilaments. Moreover, as a direct test of the hypothesis that expanding NF-M length was a mechanism utilized to increase axonal diameter and conduction velocity, I shortened the length of NF-M in mice through gene-targeting. Decreasing NF-M length resulted in mice with larger diameter axons yet the insulating myelin did not increase in thickness around the axons. This suggested that the overall length of NF-M is not required for an increase in axonal diameter. Also, myelin does not have the plasticity to compensate for changes in the growth of the axon.