Table 1. Dystonias with Established Causative Gene Defects

Locus	Designation	Inheritance	Gene Product
DYT1	primary torsion dystonia	AD	torsinA
DYT5	dopa-responsive dystonia	AD	GTP cyclohydrolase 1
	Segawa syndrome	AR	tyrosine hydroxylase
DYT11	myoclonic dystonia	AD	ϵ-sarcoglycan
DYT12	rapid-onset dystonia-parkinsonism	AD	Na^+/K^+-ATPase α3 subunit

which are required for dopamine synthesis. Oxidative stress is another possible link between basal ganglionic damage and RDP. Reactive oxygen species produced in the metabolism of dopamine may contribute to the accumulation of misfolded proteins implicated in the pathogenesis of Parkinson's disease (Dauer and Przedborski, 2003). Stress is also an established trigger for the onset of RDP, which apparently involves a catastrophic irreversible event. There is no direct evidence to date, however, for specific involvement of the dopaminergic system in RDP. Symptoms in RDP do not respond to L-dopa administration, and pathological examination of a single available case did not show loss of dopaminergic neurons in the nigra. On the other hand, ample evidence is available that loss of Na^+/K^+-ATPase activity results in clinical phenotypes resulting from preferential dysfunction of the CNS. Partial inhibition of sodium pump activity in rat brain causes hyperexcitability and epileptiform bursts (Vaillend et al., 2002). Total absence of the α2 subunit in mice is neonatal lethal, whereas heterozygous mice have enhanced fear responses and neuronal activity in the amygdala (Ikeda et al., 2003). In man, haploinsufficiency due to missense mutations in the α2 subunit (*ATP1A2*) is associated with susceptibility to familial hemiplegic migraine and benign familial infantile convulsions (Vanmolkot et al., 2003). As reported in this issue, missense mutations in the α3 subunit (*ATP1A3*) predispose to rapid-onset dystonia-parkinsonism. These genotype-phenotype correlations, between mutations of a specific α subunit gene and distinct clinical syndromes, illustrate the importance of isoform specificity of the Na^+/K^+-ATPase in normal brain function and serve as an impetus for further study.

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New Roles for an Old Molecule in Axon-Glial Interaction

Axons need to be above a minimum size before they can be ensheathed by myelin-forming glia. But it has generally been assumed that the axonal signals that initiate myelination, whatever they are, would act similarly in both the CNS and the PNS. The surprising finding of Chan et al. in this issue of *Neuron* is that NGF can act as a regulator of ensheathment but that it has opposite effects on CNS and PNS axons.

The evolutionary success of vertebrates has been strongly underpinned by the acquisition of myelinated nerve fibers. Without the rapid rates of nerve conduction that myelin confers, it is difficult to conceive how complex yet compact nervous systems could have developed. Although oligodendrocytes and Schwann cells, the myelin-forming glial cells of the CNS and PNS, respectively, are well characterized, some major mechanistic questions concerning the cell biology of axon-glial interaction have been outstanding. These include (1) how is myelin thickness tailored to the diameter of the axon, (2) what determines the optimum length of each myelin segment, and (3) why are some nerve fibers myelinated while others simply remain surrounded by glial processes? It looks like 2004 will mark a significant watershed in our understanding of two of these important questions. First, neuregulin-1 has been shown to regulate myelin thickness (Michailov et al., 2004), and now Chan et al. (2004) show in this issue of *Neuron* that

neurotrophins have a role in modulating the receptiveness of axons to glial ensheathment.

The prototypic neurotrophin is nerve growth factor (NGF), and studies on the ability of NGF to promote neuron survival have a venerable history (Levi-Montalcini and Cohen, 1960). Other neurotrophins and their cognate Trk and $p75^{NTR}$ receptors are known to have distinct roles in the development of glia. Neurotrophin-3 (NT3) influences both the survival of oligodendrocytes and the proliferation of their precursors (Barres et al., 1994), and brain-derived neurotrophic factor (BDNF) and NT3 have opposing effects on Schwann cell myelination (Cosgaya et al., 2002). The effects of NT3 on oligodendrocytes are direct, whereas it is not certain whether the effects of BDNF and NT3 are mediated by receptors on neurons or on Schwann cells. Now it appears that NGF also has a role in regulating myelination (Chan et al., 2004). Interestingly, the effects of NGF on the cell biology of myelin-forming glia appear to be indirect, i.e., the signals that affect myelination emanate from axons in response to the binding of NGF to axonal TrkA receptors.

In a series of elegant experiments, Chan et al. have made extensive use of myelinating cocultures in which they used the neurites extended by dorsal root ganglion (DRG) neurons as the substrate for myelination by either Schwann cells or oligodendrocytes. Crucially, they first "weaned" the DRG neurons from dependency on NGF to an independent state. This then allowed them to test the effect of NGF on myelination. Remarkably, NGF stimulated myelination by Schwann cells but inhibited oligodendrocyte-mediated myelination. Blocking experiments showing that NGF had its effect at TrkA receptors were confirmed by the use of reagents that can independently activate these receptors. The importance of TrkA receptors in mediating the action of NGF was underscored by the fact that the myelination of a subpopulation of DRG neurons that are dependent on BDNF for survival was unaffected by NGF. This in turn raises the question as to what signals are used by those neurons that don't express TrkA receptors. A related question is how those peripheral axons that project from TrkA-positive neurons and enter the spinal cord can be myelinated by both Schwann cells in the PNS and oligodendrocytes in the CNS. A possible explanation advanced by Chan et al. is that the timing of myelination in the CNS and PNS may be in sync with complementary changes in the local levels of NGF.

In vertebrates, large diameter axons are myelinated, whereas thin axons, though surrounded by glial processes, resist myelination. It is possible that NGF could influence the diameter of responsive axons, but this would still leave open the question as to why myelin-forming glia can recognize differences in axonal size. Nevertheless, these observations have firmly established the importance of the properties of the axon itself as a determinant of myelination. This is of particular relevance in the context of demyelinating diseases such as multiple sclerosis (MS), where it has been proposed that changes in the expression of proteins on the surface of axons might make them more or less susceptible to remyelination (Charles et al., 2002). Even in axons that express TrkA, it seems that responsiveness to NGF cannot be the whole story, since the thin sensory C fibers of the PNS possess TrkA receptors but they are not myelinated.

The fact that Chan et al. were able to show that NGF appears to act via axonal not glial TrkA receptors leads to an important question that future work will need to address, namely, what is the nature of the axonal signals that influence the cell biology of oligodendrocytes and Schwann cells that are produced in response to the binding of NGF to axons? Ligand binding to Trk receptors causes autophosphorylation and the subsequent binding of various adaptor proteins, including PLC-γ-1, SHC, PI-3 kinase, and Erk 1. Each of these has been implicated in signaling pathways that converge on the nucleus. Hence, it is very likely that receptor activation influences the transcription of neuronal genes that can modulate the ability of oligodendrocytes and Schwann cells to myelinate. Possible candidates for the effector molecules produced by neurons might include secreted molecules such as neuregulins or the compounds known to act at glial purinergic receptors (Fields and Stevens-Graham, 2002). Axonal cell adhesion molecules are also reasonable candidates. Some of the best-characterized axo-glial cell adhesion molecules are the neuronal proteins Caspr and Contactin and the glial isoform of Neurofascin, NF155 (Poliak and Peles, 2003; Salzer, 2003). It will be interesting to see if, in the context of axon-glial interaction, Caspr and Contactin fall out of the inevitable screens for the target genes of TrkA receptor activation.

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