Role of Axonal Transport in Neurodegenerative Diseases*

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Annu. Rev. Neurosci. 2008. 31:151–173

First published online as a Review in Advance on April 2, 2008

The *Annual Review of Neuroscience* is online at neuro.annualreviews.org

This article's doi: 10.1146/annurev.neuro.31.061307.090711

0147-006X/08/0721-0151$20.00

*This review is dedicated to Steven Ackerley who tragically died on 14 January 2008.

Key Words

amyotrophic lateral sclerosis, motor neuron disease, Charcot-Marie-Tooth disease, Alzheimer's disease, Huntington's disease, Parkinson's disease

Abstract

Many major human neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS), display axonal pathologies including abnormal accumulations of proteins and organelles. Such pathologies highlight damage to the axon as part of the pathogenic process and, in particular, damage to transport of cargoes through axons. Indeed, we now know that disruption of axonal transport is an early and perhaps causative event in many of these diseases. Here, we review the role of axonal transport in neurodegenerative disease.

Contents

AXONAL TRANSPORT

Intracellular transport of protein and organelle cargoes is an essential requirement for all mammalian cells, but this is the case especially for neurons. Neurons are polarized with axons and dendrites, and because most neuronal proteins are synthesized in cell bodies, mechanisms are required to direct axonal vs. dendritic transport. In addition, the distances over which cargoes have to be moved are longer than in other cell types (a human motor neuron axon can exceed 1 m). Finally, even within an individual axon, cargoes must be targeted to specific compartments, e.g., sodium channels are enriched at nodes of Ranvier, whereas synaptic proteins are targeted to the axon terminal. Thus the architecture of neurons makes them particularly dependent on intracellular transport processes.

Axonal transport: the movement of protein and organelle cargoes through axons

The main mechanism to deliver cellular components to their action site is long-range microtubule-based transport. The two major components of the transport machinery are the "engines," or molecular motors (**Figure 1**; see sidebar on Molecular Motors), and microtubules, the "rails" on which they run. Microtubules are polarized; the faster-growing end is referred to as the plus end and the slower growing end as the minus end. In axons, microtubule orientation is nearly uniform, with the plus ends pointing toward the synapse and the minus ends facing the cell body. As most molecular motors of the kinesin family unidirectionally move toward the microtubule plus end, they mostly mediate transport toward the synapse (anterograde). In contrast, the molecular motor cytoplasmic dynein moves toward the microtubule minus end and, accordingly, mediates transport of most cargoes toward the cell body (retrograde).

Classically, axonal transport is divided into fast and slow axonal transport on the basis of the bulk speeds of cargo movement; cargoes such as vesicles and mitochondria move by fast axonal transport at speeds of ~1 μm/s, whereas cytoskeleton components move in slow axonal transport at speeds of ~1 mm/day. However, it is now clear that both fast and slow axonal transport are mediated by the same "fast" molecular motors kinesin and cytoplasmic dynein and that the slower overall rate of slow axonal transport is due to prolonged pauses between movements (Roy et al. 2000, Wang et al. 2000).

AXONAL TRANSPORT AND NEURODEGENERATIVE DISEASE

Axonal and cell body accumulations of organelles and other proteins are hallmark pathologies for many human neurodegenerative diseases. Tau is present in the paired helical filaments (PHFs) of Alzheimer's and related diseases, α-synuclein is the principal component of Lewy bodies in Parkinson's disease, neurofilament accumulations are seen in amyotrophic lateral sclerosis (ALS), and more recently, TDP-43 accumulations have been

observed in ALS and frontotemporal lobar degeneration (Ballatore et al. 2007, Neumann et al. 2006, Spillantini et al. 1997, Xiao et al. 2006). Furthermore, axonal swellings and spheroids have been described in a number of neurodegenerative diseases (Coleman 2005). Together, such pathologies suggest that defective functioning of the axon contributes to disease and, in particular, that damage to axonal transport may underlie the pathogenic accumulation of organelles. Indeed, we now have evidence that this is the case for many neurodegenerative diseases.

The mechanisms by which axonal transport is disrupted in disease are varied. Like a train journey, disruption to transport can occur via damage to the engines (kinesin and cytoplasmic dynein) (**Figure 1**), damage to the rails (microtubules) (**Figure 2**), damage to the cargoes (for example, to inhibit their attachment to motors) (**Figure 3**), and damage to the ATP fuel supply for the engines (mitochondria) (**Figure 4**). In fact, all these insults can contribute to neurodegeneration. Below we describe evidence linking defective axonal transport and disease.

MOLECULAR MOTORS

Molecular motors generate force from ATP hydrolysis to move cargoes along cytoskeleton tracks. The main microtubule-based motors are members of the kinesin superfamily (45 in humans) and cytoplasmic dynein (**Figure 1**).

Kinesin-1 (also known as KIF5) is the most studied and is a heterotetramer of two kinesin heavy chains (KHC) and two kinesin light chains (KLC). KHC is composed of the catalytic motor domain, a short neck linker region, the α-helical coiled-coil stalk that is interrupted by two hinge regions, and the tail. The motor domain binds microtubules, contains the ATPase activity, and, together with the neck, confers processivity and directionality; the stalk is involved in dimerization; the tail, together with KLC, binds cargo and regulates motor activity (Hirokawa & Takemura 2005).

Cytoplasmic dynein is a multisubunit complex that contains two heavy chains that are associated with intermediate chains, light intermediate chains, and light chains. The heavy chains harbor ATPase activity and bind microtubules, whereas the other chains are involved in cargo binding and binding to dynactin. Dynactin is a protein complex that contains $p150^{Glued}$, p62, dynamitin, actin-related protein 1, CapZα and CapZβ, p27, and p24. Dynactin is a processivity factor for dynein and is implicated in cargo binding (Pfister et al. 2006).

MOTOR NEURON DISORDERS

Axonal transport defects are perhaps best characterized for motor neuron disorders. These disorders include ALS, distal hereditary motor neuropathy, spinal muscular atrophy (SMA), and hereditary spastic paraplegia (HSP).

Amyotrophic Lateral Sclerosis

Although most forms of ALS are sporadic, ~10% of cases are familial, and evidence now implicates mutations in 5 genes as causative for the disorder (Pasinelli & Brown 2006). Some of these disease mutants damage axonal transport.

Mutant SOD1. Mutations in the gene encoding Cu/Zn superoxide dismutase-1 (SOD1) cause ~20% of familial ALS cases. Expression of mutant SOD1 in transgenic mice induces motor neuron disease (MND), and analyses of such mice reveal that damage to axonal transport is an early pathogenic event (De Vos et al. 2007, Kieran et al. 2005, Williamson & Cleveland 1999, Zhang et al. 1997). The early nature of this damage argues that damage to axonal transport contributes to the disease process in a primary fashion and is not just an end-stage epiphenomenon. Mutant SOD1 damages both fast and slow axonal transport (De Vos et al. 2007, Williamson & Cleveland 1999, Zhang et al. 1997). However, mutant SOD1 differentially affects axonal transport of specific cargoes. Anterograde movement of the cytoskeleton including neurofilaments is slowed, fast transport of vesicles is inhibited in both anterograde and retrograde directions but inhibition of mitochondrial movement is anterograde specific (De Vos et al. 2007, Williamson & Cleveland 1999, Zhang et al. 1997).

SOD1: Cu/Zn superoxide dismutase-1

MND: motor neuron disease

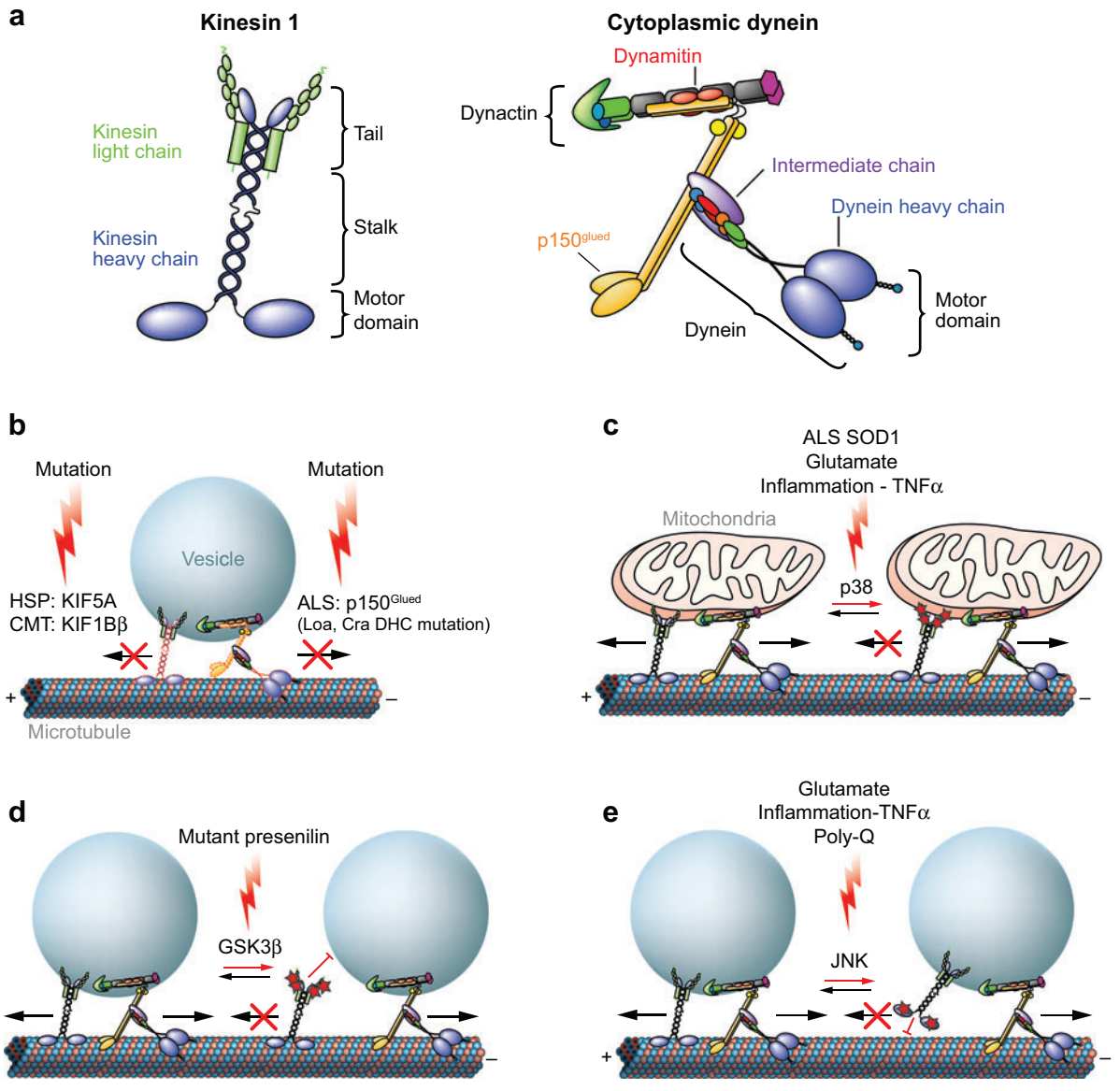

Figure 1

Mechanisms of axonal transport defects: damage to molecular motors. (*a*) Kinesin and cytoplasmic dynein are the main microtubule-based motors. (*b*) Mutations in kinesins or cytoplasmic dynein that inhibit their activity (or are predicted to do so) cause some familial forms of ALS ($p150^{Glued}$), hereditary spastic paralegia (HSP) (KIF5A), and Charcot-Marie-Tooth disease (CMT) (KIF1Bβ). Furthermore, Loa and Cra mice that carry mutations in dynein heavy chain (DHC) exhibit axonal transport defects and develop MND. Phosphorylation (*stars*) of kinesin 1 inhibits its activity at multiple levels. (*c*) Phosphorylation of KLC by a p38-dependent pathway inhibits mitochondria-bound kinesin 1 activity without affecting its binding to microtubules or mitochondria. (*d*) By contrast, mutant presenilin-induced phosphorylation of KLC by GSK3β inhibits kinesin 1–mediated transport of vesicles by disrupting attachment of kinesin 1 to vesicles. (*e*) Finally, phosphorylation of KHC by JNK inhibits kinesin 1–mediated vesicle transport by impeding the interactions of KHC with microtubules; JNK is activated by disease-associated signals including expanded polyglutamines (Poly-Q). Cytoplasmic dynein activity may also be regulated by phosphorylation. However, we do not know if this plays a role in neurodegeneration.

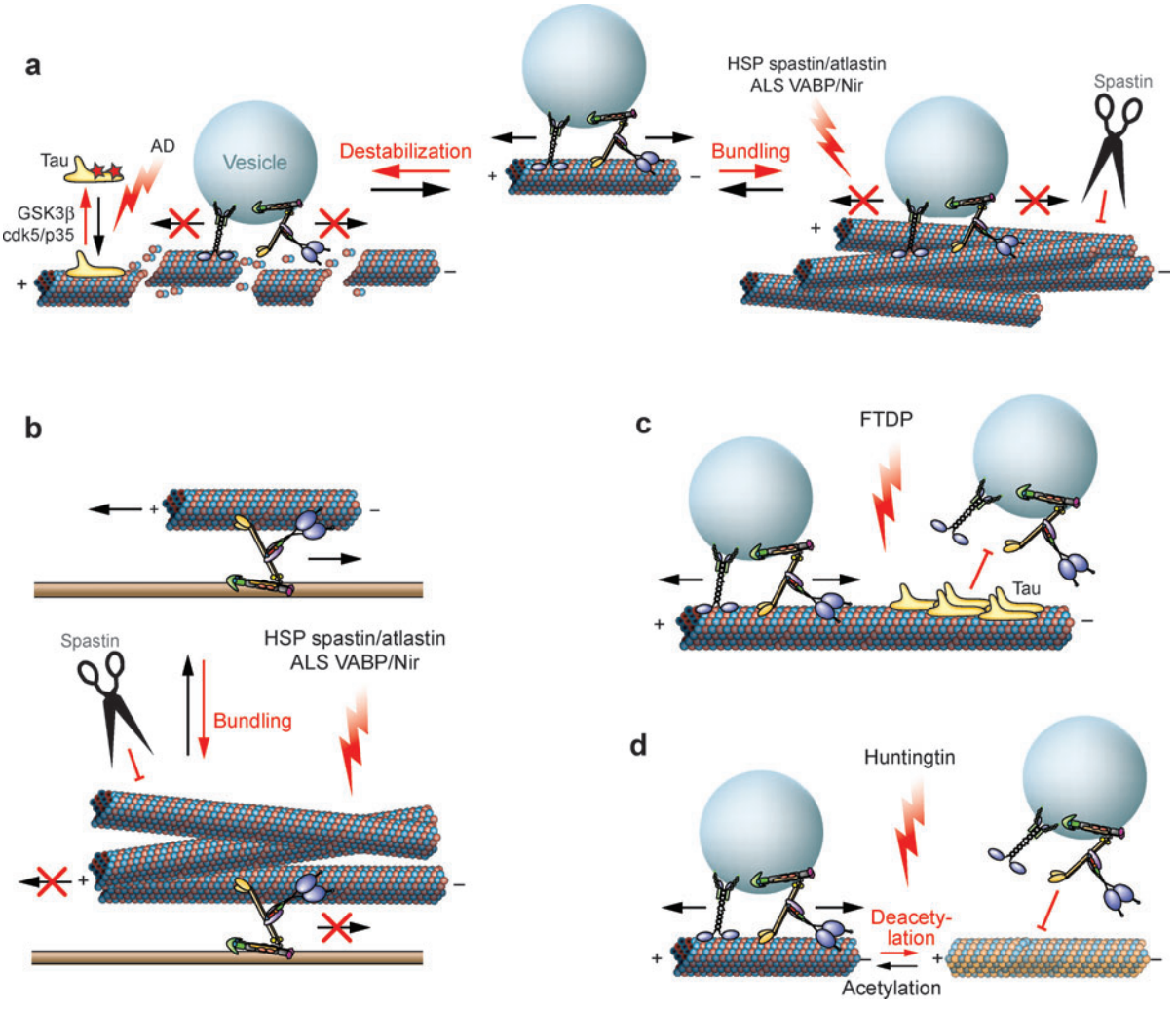

Figure 2

Mechanisms of axonal transport defects: damage to microtubules. Microtubules are highly dynamic structures that undergo rapid periods of growth and shrinkage, and their dynamic behavior is regulated by several mechanisms. Deregulation of these dynamic properties may lead to disruption of cargo transport. (*a*) Destabilization of microtubules by decreased binding of GSK3β and/or cdk5/p35-induced hyperphosphorylated tau may lead to a loss of microtubule "rails" for transport (*left*). Loss-of-function mutant spastin and mutant VAPB induce abnormal bundling of microtubules to misdirect transport (*right*).
(*b*) Because short microtubules are preferentially transported, mutant spastin/atlastin and VAPB may damage axonal transport of microtubules themselves. This could happen via inhibition of microtubule severing by mutant spastin or microtubule bundling by VAPB/Nir. (*c*) FTDP tau may damage transport by interfering with the interaction of kinesin 1 with microtubules. (*d*) Finally, mutant huntingtin may induce deacetylation of α-tubulin and subsequent release of motors from microtubules.

How mutant SOD1 perturbs axonal transport is not fully understood, but it is likely that it involves several different pathways. These mutant SOD1-induced pathways may include damage to mitochondria and reduced ATP supply to molecular motors, pathogenic signaling that alters phosphorylation of molecular motors, and altered phosphorylation of cargoes such as neurofilaments to disrupt their association with motors.

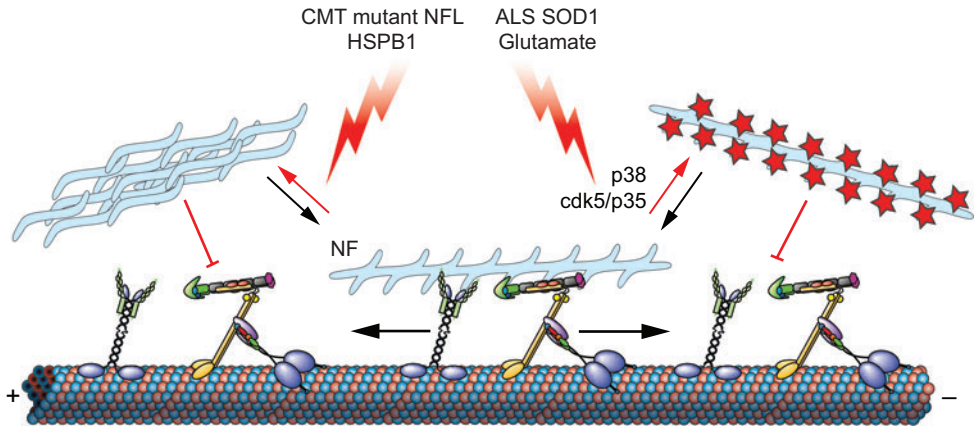

Figure 3

Mechanisms of axonal transport defects: damage to cargoes. Regulation/disruption of motor-cargo interaction may disrupt axonal transport in a number of neurodegenerative diseases. Phosphorylation (*stars*) of neurofilaments (NF) by p38 and/or cdk5/p35 kinases slows their transport, possibly by preventing attachment of molecular motors (*right*). Alternatively, misassembly of NF by mutations in CMT mutant NFL or the NF chaperone HSP1B may disrupt their interaction with molecular motors and cause their defective axonal transport (*left*).

Damage to mitochondria. Many studies have demonstrated that mutant SOD1 selectively associates with and damages mitochondria (see Boillee et al. 2006). This damage is believed to severely impair the mitochondrial electron transfer chain and ATP synthesis (Mattiazzi et al. 2002). Damage to mitochondria has been linked to a reduction in their anterograde transport (Miller & Sheetz 2004), and recently, De Vos et al. (2007) presented formal evidence that mutant SOD1 perturbs mitochondrial anterograde movement. Inhibition of anterograde mitochondrial transport leads to a net increase in their retrograde transport, which results in depletion of mitochondria from axons. This could adversely affect axonal transport of other cargoes because of diminished ATP levels (**Figure 4**) (De Vos et al. 2007).

Inflammatory signals. Although studies of isolated motor neurons in culture have shown that mutant SOD1-induced damage to axonal transport can be neuron specific (De Vos et al. 2007, Kieran et al. 2005), elegant experiments involving chimeric mutant SOD1 mice and mice with a deletable mutant *SOD1* gene have demonstrated that other cell types contribute to disease. Thus, although expression of mutant SOD1 in motor neurons is a primary determinant of disease onset, expression in microglia markedly influences disease progression (see Boillee et al. 2006). Inflammatory responses have been strongly linked to ALS, and mutant SOD1 itself can be secreted and activate microglia (Beers et al. 2006, Nguyen et al. 2004, Urushitani et al. 2006). Also, the anti-inflammatory agent minocycline is protective in mutant SOD1 transgenic mice (Kriz et al. 2002, Van Den Bosch et al. 2002, Zhu et al. 2002). Inflammatory signals from neighboring cells may therefore provide additional insults to axonal transport. Indeed, tumor necrosis factor-α (TNFα) signaling inhibits kinesin function via p38 stress-activated kinase-dependent phosphorylation of kinesin (**Figure 1**) (De Vos et al. 2000), and p38 is activated in mutant SOD1 transgenic mice (Ackerley et al. 2004, Raoul et al. 2002, Tortarolo et al. 2003).

Excitotoxic signaling. Excitotoxic insults likely contribute to ALS because alterations to proteins and metabolites involved in glutamate handling are seen in sporadic ALS cases (Van Den Bosch et al. 2006). Moreover, mutant

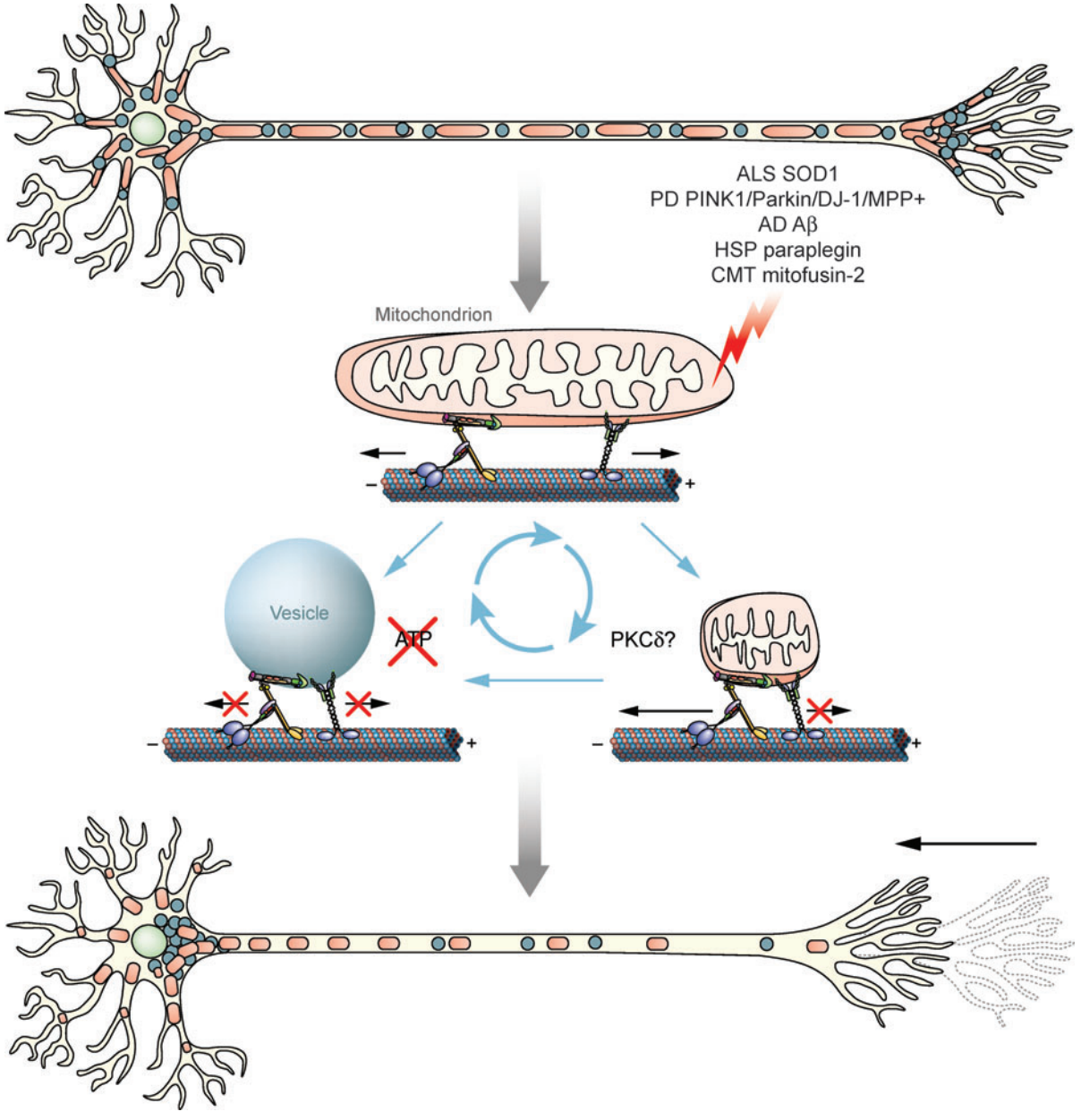

Figure 4

Mechanisms of axonal transport defects: damage to mitochondria. Damage to mitochondria is seen in many neurodegenerative diseases. Mitochondrial dysfunction likely affects axonal transport in at least two ways. First, inhibition of mitochondrial function reduces anterograde transport of both mitochondria and vesicles possibly by activating PKCδ. Second, the resulting diminution of mitochondria in axons will likely decrease ATP supply to molecular motors leading to decreased anterograde and retrograde movement of other axoplasmic cargoes. As mitochondrial dysfunction also reduces ATP production, the latter might be part of a vicious circle mechanism that ultimately leads to dying-back of axons.

JNKs: c-Jun-N-terminal kinases

SOD1 selectively damages the glial glutamate transporter EAAT2 (which removes synaptic glutamate), and EAAT2 levels are reduced in mutant SOD1 transgenic mice (Bruijn et al. 1997, Trotti et al. 1999). Excitotoxicity may therefore contribute to the pathogenic process in both sporadic and mutant SOD1 familial forms of ALS.

Two studies have now shown that excitoxic application of glutamate damages axonal transport (Ackerley et al. 2000, Hiruma et al. 2003). The mechanisms involved could damage both motors and cargoes. In particular, glutamate activates JNKs, p38, and cdk5/p35 (Ackerley et al. 2000, Brownlees et al. 2000, Kawasaki et al. 1997, Lee et al. 2000, Schwarzschild et al. 1997), and all are strongly linked to axonal transport. Thus JNKs and p38 phosphorylate kinesin heavy and light chains, respectively, to inhibit transport (**Figure 1**) (De Vos et al. 2000, Morfini et al. 2006), and JNKs, p38, and cdk5/p35 all phosphorylate neurofilament medium chain (NFM)/neurofilament heavy chain (NFH) sidearms, a process that is linked to slowing of neurofilament transport (**Figure 3**) (see below).

Damage to cargoes. Finally, mutant SOD1 may damage cargoes to inhibit their transport (possibly by promoting their release from motors) (**Figure 3**). One cargo that is intimately linked to ALS is neurofilaments. Neurofilament accumulations are a hallmark pathology of ALS, and overexpression of neurofilament light (NFL) and heavy (NFH) chain proteins, peripherin (a further neuronal intermediate filament protein), or a mutant NFL that disrupts neurofilament assembly induces MND in transgenic mice (Beaulieu et al. 1999, Cote et al. 1993, Lee et al. 1994, Xu et al. 1993). Moreover, axonal transport is defective in these neurofilament transgenics (Collard et al. 1995, Millecamps et al. 2006). Such overexpression of individual NF subunits likely alters neurofilament assembly properties to disrupt transport because proper assembly is required for transport (Millecamps et al. 2006, Yuan et al. 2003). Direct evidence to link mutant SOD1 toxicity with neurofilaments comes from experiments in which mutant SOD1 transgenic mice have been crossed with neurofilament transgenics. Modulating neurofilament expression in this way markedly alters disease onset (Couillard-Després et al. 1998, Williamson et al. 1998). Notably, deletion of NFM and NFH sidearm domains is strongly protective against mutant SOD1 disease (Lobsiger et al. 2005). The pathological neurofilament accumulations seen in ALS are aberrantly hyperphosphorylated on these NFM/NFH sidearm domains, and such phosphorylation slows neurofilament transport (Ackerley et al. 2003, Shea et al. 2004). This probably occurs by promoting neurofilament release from molecular motors (Jung et al. 2005, Wagner et al. 2004). p38 and cdk5/p35 phosphorylate NFM/NFH sidearms (Ackerley et al. 2004, Guidato et al. 1996, Sun et al. 1996), and both are activated in mutant SOD1 transgenic mice (Ackerley et al. 2004, Nguyen et al. 2001, Raoul et al. 2002, Tortarolo et al. 2003).

Mutant dynactin and disruption to cytoplasmic dynein function. The finding that mutations in the dynactin subunit $p150^{Glued}$ cause disease demonstrates a direct role of molecular motor dysfunction in ALS (**Figure 1**) (Munch et al. 2005, Puls et al. 2003). One mutation lowers the affinity of $p150^{Glued}$ for both microtubules and EB1 and may cause a loss of dynactin/dynein function and a gain of toxic function (Levy et al. 2006). The effects of additional mutations on cytoplasmic dynein function and axonal transport have not so far been described. Other evidence for a role of defective cytoplasmic dynein function in ALS involves the Loa and Cra mouse mutants and transgenic mice that express dynamitin; these animals develop MND (Hafezparast et al. 2003, LaMonte et al. 2002). The Loa and Cra mutations are in dynein heavy chain and are associated with defective retrograde transport (Hafezparast et al. 2003, Kieran et al. 2005). Expression of dynamitin perturbs dynein-dynactin interaction and, as such, dynein function (LaMonte et al. 2002).

Loa mice have been crossed with mutant SOD1 transgenics, and the phenotype is unexpected. Rather than accelerating disease progression, the presence of both mutant proteins is protective. Moreover, defective retrograde transport is partially corrected in the double mutant (Kieran et al. 2005). Although the mechanisms that underlie this effect are not clear, one possibility is that the Loa mutation counterbalances the increase in net retrograde transport of mitochondria induced by mutant SOD1 (De Vos et al. 2007). Thus, although mutant SOD1 may damage mitochondria, the mitochondria remain within axons to provide at least some ATP fuel for axonal function and transport.

ALS2/Alsin and VAPB. ALS2 and VAPB are mutated in some rare forms of ALS, and both are linked to vesicle trafficking within neurons. ALS2 is a guanine nucleotide exchange factor for both Rab5 and Rac (Jacquier et al. 2006, Otomo et al. 2003, Topp et al. 2004, Tudor et al. 2005); Rab5 functions in retrograde endosome transport (Deinhardt et al. 2006). Although ALS2 knockout mice (predicted to model ALS2 forms of ALS) have a mild phenotype, they display defects in endosomal trafficking consistent with a role in axonal transport (Devon et al. 2006, Hadano et al. 2005).

VAPB too is thought to have a role in membrane transport, particularly from endoplasmic reticulum (ER)/Golgi to the synapse (Skehel et al. 2000). VAPB also associates with microtubules, and evidence demonstrates that it has a role in microtubule organization via its interacting partner Nir (**Figure 2**) (Amarilio et al. 2005, Pennetta et al. 2002). In this context, it is noteworthy that a mutation in the tubulin chaperone Tbce, which alters microtubule organization, causes MND in the pmn mouse (Bommel et al. 2002, Martin et al. 2002).

Distal Hereditary Motor Neuropathy

Mutations in two small heat-shock proteins (HSPB1 and HSPB8) cause a form of MND that affects primarily lower motor neurons (Evgrafov et al. 2004, Irobi et al. 2004). The small heat-shock proteins perform many functions including chaperoning activity but are particularly important in responding to cellular stresses. HSPB1 and HSPB8 interact with several intermediate filament proteins to facilitate formation of properly organized neurofilament networks, and mutant HSPB1 disrupts neurofilament assembly (Evgrafov et al. 2004). Direct analyses of the effect of mutant HSPB1 on axonal transport has shown that it disrupts movement of a number of cargoes including neurofilaments (**Figure 3**) (Ackerley et al. 2006).

Spinal Muscular Atrophy

SMA is the consequence of mutations within the survival of motor neuron 1 (*SMN1*) gene (Monani 2005). *SMN1* is ubiquitously expressed and has at least two functions. One is in the assembly and regeneration of spliceosomal small nuclear ribonucleoproteins (snRNPs), a task it presumably carries out in most cell types, but the other is linked to transport of specific mRNAs through axons (Rossoll et al. 2003).

Although most axonal proteins are synthesized within cell bodies and then transported through axons, a proportion are synthesized locally within the axon/axon terminal following mRNA transport (Kiebler & Bassell 2006). β-actin is one such mRNA and functions within the growth cone to promote axonal outgrowth. Loss of SMN leads to reduced axonal outgrowth that correlates with reductions in both β-actin mRNA and protein in the growth cone (Rossoll et al. 2003). Also, the SMN binding partner hnRNP-R binds to the 3′-UTR of β-actin mRNA, and so SMN may be complexed with β-actin mRNA (Rossoll et al. 2003). Thus, SMN may function in axonal transport of actin and other mRNAs, and its loss in SMA might induce disease as a consequence of disrupted mRNA transport. Defective axonal transport of RNA complexes has also been linked to another neurological disease, Fragile X syndrome. The Fragile X mental retardation protein is also present in RNA granules and has been linked

Retrograde axonal transport: movement of cargoes toward the cell body

to transport of several RNAs including that for β-actin (see Kiebler & Bassell 2006).

Hereditary Spastic Paraplegia

HSP is a group of heterogeneous hereditary neurological disorders that affect upper motor neurons. Thirty genetic loci have been linked to HSP and 15 responsible mutant genes so far identified (Fink 2006). Some of these mutants have been shown to, or are highly likely to, disrupt axonal transport, although the mechanisms involve a variety of insults.

Damage to kinesin. Mutations in kinesin 1 are the cause of a few rare forms of HSP (**Figure 1**). Four causative mutations have been described and, though not functionally tested, all are likely to influence motor function because they involve conserved residues in either the motor head domains or the coiled-coil stem region (Reid 2003).

Damage to microtubules. Mutations in the gene encoding spastin are responsible for 40% of autosomal dominant HSP cases. A range of mutations throughout the protein causes disease, and whereas some may represent loss-of-function mutants, others may act in a dominant-negative fashion. Spastin is part of a small family of AAA proteins that function to sever and bundle microtubules (Roll-Mecak & Vale 2005, Salinas et al. 2005). By severing microtubules, spastin likely plays a role in axonal transport; recent experimental studies support this hypothesis and the notion that HSP mutant spastin is defective in the process (McDermott et al. 2003, Tarrade et al. 2006). How mutant spastin might perturb axonal transport is not fully clear. One possibility is that the mutants alter the microtubule rails to disrupt movement of cargo-carrying motors (**Figure 2**). However, another possibility is that mutant spastin disrupts transport of microtubules themselves. The length of microtubules is related to their potential to be transported through axons; long microtubules are essentially stationary, whereas shorter ones move bidirectionally (Ahmad et al. 2006, Baas et al. 2005, Wang & Brown 2002). Defective microtubule severing by mutant spastin may therefore block microtubule transport (**Figure 2**). Ultimately, this may damage axonal transport of other cargoes. Spastin also binds to membrane proteins of the endoplasmic reticulum and endosomes, so one possibility is that it functions in regulating subsets of microtubules responsible for axonal transport of endoplasmic reticulum/endosomes (Reid et al. 2005). Mutations in the gene encoding atlastin are responsible for further forms of HSP, and atlastin binds to spastin; thus mutant atlastin may also damage axonal transport (Evans et al. 2006, Sanderson et al. 2006).

Mutations in NIPA1 that cause a dominant pure form of HSP have also been linked to defective axonal transport. The *Drosophila* homologue is termed spichthyin, localizes to early endosomes, and regulates growth of the neuromuscular junction via inhibition of bone morphogenetic protein (BMP)-transforming growth factor-β signaling. In the fly, BMP signaling regulates microtubule dynamics and axonal transport, and spichthyin inhibits these functions (Wang et al. 2007). Thus, mammalian NIPA1 may also function in microtubule maintenance and axonal transport.

Damage to mitochondria. Loss-of-function mutations in the *SPG7* gene encoding the mitochondrial ATPase paraplegin disrupt axonal transport. Paraplegin-deficient mice have distal axonopathy of spinal and peripheral axons. Morphological abnormalities include abnormal hypertrophic mitochondria and, later, axonal swellings containing massive accumulation of organelles and neurofilaments that are consistent with a defect in axonal transport of these cargoes. Indeed, neurotracer studies reveal that the mice have a defect in retrograde axonal transport (Ferreirinha et al. 2004).

Damage to myelination. Mutations in the proteolipid protein 1 (*PLP1*) gene that encodes PLP and DM20, the major proteins of the myelin sheath, are responsible for X-linked HSP2. Mice in which PLP1 has been deleted

are a model for some forms of HSP2. These animals exhibit axonal accumulations of mitochondria and other membranous organelles that are consistent with a disruption to axonal transport and show defective retrograde transport of labeled cholera toxin (Edgar et al. 2004). Many studies have demonstrated a link between myelination and axonal transport (e.g., de Waegh & Brady 1990, de Waegh et al. 1992, Sanchez et al. 2000). Although the mechanisms are not fully understood, myelin probably signals to induce changes to phosphorylation of a number of axonal proteins associated with transport. Neurofilaments are one such protein (de Waegh et al. 1992, Garcia et al. 2003). Defective myelination also causes some forms of Charcot-Marie-Tooth (CMT) disease (see below).

ALZHEIMER'S DISEASE AND RELATED DISORDERS

Two of the hallmark pathologies of Alzheimer's disease are neurofibrillary tangles containing paired helical filaments (PHFs) and amyloid plaques. PHFs are assembled from hyperphosphorylated tau, a microtubule-associated protein; amyloid plaques are areas of degenerating neurites surrounding a core of amyloid-β peptide (Aβ). Aβ is a 40-42 amino acid peptide that is derived by proteolytic cleavage from a larger precursor protein, APP. The Aβ and tau pathologies are central to the pathogenesis of Alzheimer disease and analyses of genetic forms of Alzheimer's disease, and some related frontotemporal dementias support this notion. Thus, mutations and duplication of the *APP* gene and mutations in the presenilin genes (components of the γ-secretase complex involved in cleaving Aβ from APP) cause some familial forms of Alzheimer's disease. At least some of these genetic lesions increase production of Aβ or the relative proportion of Aβ(1-42) to Aβ(1-40); the longer Aβ(1-42) form is believed to be pathogenic. Additionally, mutations in the *tau* gene are responsible for some familial forms of fronto-temporal dementia with Parkinsonism (FTDP) (Hardy 2006).

Axonal transport defects have now been described as an early pathological feature in a variety of animal models of Alzheimer's disease and tauopathies. These include transgenic mouse models overexpressing APP or familial Alzheimer's disease mutant APP (Salehi et al. 2006, Stokin et al. 2005), mutant presenilin-1 (Lazarov et al. 2007), and both wild-type and FTDP mutant tau (Ishihara et al. 1999, Zhang et al. 2004). The mechanisms by which these different genetic insults disrupt axonal transport are not properly understood. Aβ itself disrupts transport of a variety of cargoes including mitochondria (Hiruma et al. 2003, Rui et al. 2006). Indeed, Aβ associates with and may damage mitochondria (**Figure 4**) (Manczak et al. 2006). As such, mutant APP and presenilin-1 may damage transport by altering neurotoxic Aβ production. However, evidence also shows that mutant presenilin-1 impairs transport via an effect on kinesin 1 motor function because it activates the KLC2 kinase glycogen synthase kinase-3β (GSK3β), which leads to a release of cargo from motors (**Figure 1**) (Pigino et al. 2003).

Both wild-type and FTDP tau also disrupt axonal transport of multiple cargoes (Stamer et al. 2002, Zhang et al. 2004). One possibility is that tau interferes with kinesin binding to microtubules to damage transport (**Figure 2**) (Seitz et al. 2002). However, tau is also involved in stabilizing microtubules, and hyperphosphorylated tau (such as in PHF) has a reduced affinity for microtubules and is less potent at stabilizing them (Wagner et al. 1996). Hyperphosphorylation of tau by GSK3β and/or cdk5/p35 in Alzheimer's disease (Lovestone et al. 1994, Patrick et al. 1999) may therefore lead to a loss of microtubule rails for axonal transport. As such, both loss and gain of tau function may disrupt axonal transport (**Figure 2**).

Disruption to anterograde axonal transport (including that of APP) via a depletion of KLC1 increases Aβ production, although the precise mechanisms that underlie this effect are unclear (Stokin et al. 2005). BACE1, the rate-limiting enzyme in APP processing to produce Aβ is

APP: amyloid precursor protein

γ-secretase: cleaves APP at the C-terminus of the Aβ sequence. It comprises at least four proteins (presenilin-1/2, Aph1, Pen2, and Nicastrin).

KLC: kinesin light chain

Anterograde axonal transport: movement of cargoes toward the synapse

Secretases: enzymes that cleave APP

KHC: kinesin heavy chain

most active in an acidic environment, and as such, a significant proportion of Aβ is produced in endosomes and lysosomes (Wilquet & De Strooper 2004). Thus, one possibility is that defective anterograde transport alters APP trafficking so that it moves to endosomes and/or lysosomes. Whatever the precise mechanism, any primary damage to axonal transport in Alzheimer's disease is likely to be amplified by this related increase in neurotoxic Aβ.

Because disruption to anterograde axonal transport of APP increases Aβ production (Stokin et al. 2005), a proper understanding is required of the mechanism by which APP and its secretases are transported through axons. Kamal et al. (2001) proposed that APP is a ligand for KLC that facilitates axonal transport of a membranous compartment containing both BACE1 and presenilin. However, others have disputed these findings (Lazarov et al. 2005). Also, direct analyses of YFP/CFP-tagged APP and BACE1 movement in cotransfected neurons do not reveal coincident movement of the two cargoes (Goldsbury et al. 2006). A further possibility is that APP movement involves some of its binding partners. APP interacts with PTB-containing proteins, including the adaptor proteins JNK-interacting proteins (JIPs) and X11s, and these may be involved (see Miller et al. 2006). JIPs are ligands for KLC (Bowman et al. 2000, Verhey et al. 2001), and some evidence shows that APP and JIP1 are transported as a complex (Muresan & Muresan 2005). X11α interacts with the dendritic kinesin 2 family member KIF17, and both X11α and X11β bind to a further ligand for KLC1, alcadein/calsyntenin (Araki et al. 2007, Konecna et al. 2006, Setou et al. 2000). The X11s inhibit Aβ production, which may be via an effect on APP transport (Miller et al. 2006). Thus a variety of insults associated with Alzheimer's disease are now known to damage axonal transport. These insults include damage to motors (altered phosphorylation of KLC2 via mutant presenilin to release cargoes), blocking of kinesin binding to microtubules (mutant tau), and damage to mitochondria via toxic Aβ (**Figures 1**, **2**, and **4**).

HUNTINGTON'S AND OTHER POLYGLUTAMINE EXPANSION DISEASES

Some familial neurodegenerative diseases are caused by expansion of polyglutamine stretches. Such diseases include Huntington's disease, Kennedy's disease, and some spinocerebellar ataxias. In Huntington's and Kennedy's diseases, the expansions occur within the huntingtin and androgen receptor proteins, respectively, and expression of mutant huntingtin or androgen receptor proteins disrupts axonal transport in many models, including isolated squid axoplasm (Szebenyi et al. 2003), *Drosophila* (Gunawardena et al. 2003, Lee et al. 2004), and mammalian neurons (Chang et al. 2006, Gauthier et al. 2004, Trushina et al. 2004).

The mechanisms by which they damage transport are not fully understood, but the polyglutamine-expanded androgen receptor leads to phosphorylation of KHC by JNKs; this phosphorylation reduces kinesin binding to microtubules to inhibit transport (**Figure 1**) (Morfini et al. 2006). However, at least for Huntington's disease, evidence indicates other mechanisms whereby the mutants may damage transport, and some of these mechanisms involve disruption to the normal function of huntingtin. Huntingtin binds to HAP1 (huntingtin-associated protein), and HAP1 is strongly implicated in transport processes; it interacts with KLC1 (McGuire et al. 2005) and the $p150^{Glued}$ subunit of dynactin (Engelender et al. 1997, Li et al. 2001). Also, huntingtin enhances retrograde transport of brain-derived neurotrophic factor (BDNF), which involves HAP1 and dynactin, but mutant huntingtin is defective in this process (Gauthier et al. 2004).

Clearance of aggregate-prone proteins such as mutant huntingtin likely represents a key neuronal defense mechanism. One route for such clearance involves autophagosomes, and proper functioning of cytoplasmic dynein is likely essential for this process (Ravikumar et al. 2005). One possibility is that cytoplasmic dynein retrogradely transports aggregate-prone proteins to the cell body for clearance

by lysosomes. Thus, mutant huntingtin may damage retrograde transport not only of cargoes, such as BDNF, but also of toxic aggregates of itself. Finally, Dompierre et al. (2007) recently linked mutant huntingtin with axonal transport via an effect on α-tubulin acetylation. Tubulin acetylation promotes kinesin 1 binding to microtubules and stimulates axonal transport (Reed et al. 2006). Tubulin acetylation is reduced in Huntington disease brains, so mutant huntingtin may disrupt transport via an effect on microtubule acetylation (**Figure 2**) (Dompierre et al. 2007). Expanded polyglutamines may therefore disrupt axonal transport by pathological phosphorylation of KHC, and mutant huntingtin could damage transport by affecting both molecular motors and microtubules (**Figures 1** and **2**).

PARKINSON'S DISEASE

α-synuclein-containing Lewy bodies and Lewy neurites within dopaminergic neurons of the substantia nigra are principal pathologies of Parkinson's disease and related disorders (Tofaris & Spillantini 2007). Moreover, mutations or increased dosage of the α-synuclein gene are the cause of some familial forms of Parkinson's disease (Hardy et al. 2006). The mechanisms by which α-synuclein accumulates within Lewy bodies are not properly understood, but evidence now suggests that defective axonal transport of α-synuclein itself may contribute to the process. First, direct analyses of movement of wild-type and two familial Parkinson's disease-associated mutant α-synucleins through axons of cultured neurons have revealed reduced transport rates of the mutants (Saha et al. 2004). Second, serine-129 of α-synuclein is selectively hyperphosphorylated in Lewy bodies and other synucleinopathy lesions (Fujiwara et al. 2002), and mutation of this site to mimic permanent phosphorylation also reduces axonal transport of α-synuclein (Saha et al. 2004). Thus blocking axonal transport of α-synuclein may contribute to its accumulation within Lewy bodies in both sporadic and some familial cases of Parkinson's disease.

Mutant *parkin*, *PINK1*, *DJ-1*, and *LRRK2* are additional genes associated with familial forms of Parkinson's disease (Hardy et al. 2006). Although direct evidence to link these proteins with axonal transport is lacking, parkin, PINK1, and DJ-1 have all been associated with the maintenance of mitochondria and antioxidant defenses (Abou-Sleiman et al. 2006), and damage to mitochondria perturbs transport of mitochondria through axons (De Vos et al. 2007, Miller & Sheetz 2004). Moreover, inhibition of complex I of the electron transport chain with 1-methyl-4-phenylpyridinium (MPP+), the active metabolite of MPTP, which induces Parkinsonism, decreases anterograde and increases retrograde axonal transport of membranous vesicles in squid axoplasm. This effect involves caspase 3 and PKCδ activation (**Figure 4**) (Morfini et al. 2007).

CHARCOT-MARIE-TOOTH DISEASE

Charcot-Marie-Tooth disease (CMT) includes a heterogeneous group of hereditary motor and sensory neuropathies, the majority being classified as demyelinating (CMT1) or axonal (CMT2) on the basis of electrophysiology.

Axonal Forms of CMT (CMT2)

Dominantly inherited mutations in the gene encoding mitofusin 2 have been demonstrated as causative in CMT2A. Mitofusin 2 is present in the outer mitochondrial membrane and is required for mitochondrial fusion. Fibroblasts from patients and mitofusin 2 knockout mice show fragmented, dispersed mitochondria with severely reduced motility, and expression of CMT2A mutant mitofusin 2 impairs axonal transport of mitochondria in primary neurons (**Figure 4**) (Baloh et al. 2007, Chen et al. 2003). A loss-of-function mutation in the kinesin 3 family member KIF1bβ is also causative of CMT2A (Zhao et al. 2001). KIF1bβ transports some synaptic vesicles, and heterozygous KIF1bβ knockout mice develop a peripheral neuropathy (**Figure 1**) (Zhao et al. 2001).

Mutations in the small GTPase Rab7 cause CMT2B, which predominantly affects sensory neurons in patients. Rab7 regulates vesicle trafficking events from early to late endosomes in the endocytic pathway, and studies recently demonstrated its function in the retrograde axonal transport pathway for neurotrophins (Deinhardt et al. 2006). Thus CMT2B mutant Rab7 may disrupt retrograde transport. Finally, mutations in the neurofilament NFL are found in some CMT2E patients, and at least some of these disrupt neurofilament assembly and axonal transport of neurofilaments and mitochondria (**Figure 3**) (Brownlees et al. 2002, Perez-Olle et al. 2005).

Demyelinating Forms of CMT (CMT1)

Demyelinating forms of CMT are the most prevalent and often involve duplications of, or point mutations in, the peripheral myelin protein 22 gene (*PMP22*). In CMT1 patients, Schwann cells that ensheath motor and sensory axons in the peripheral nervous system show defective myelination. A wealth of data link Schwann cells with axonal transport, and indeed, PMP22 mutant Trembler mice display defective slow axonal transport of the cytoskeleton (de Waegh & Brady 1990). One suggestion is that signaling mechanisms from the Schwann cell impact the axon to alter phosphorylation of the cytoskeleton and axonal transport (Garcia et al. 2003).

MITOCHONDRIAL DAMAGE AND AXONAL TRANSPORT

Mitochondria use oxidative phosphorylation to produce ATP but as a by-product generate toxic reactive oxygen species (ROS). These ROS can damage many cellular components but also mitochondria and their DNA. Mitochondria accumulate mutations/damage over their lifetime, which results in reduced function with aging. As such, mitochondria represent a prime target for age-related toxic insults (Wallace 2005). As listed above, mitochondria are selectively targeted for damage in many neurodegenerative diseases that involve defective axonal transport. Mutations in the mitochondrial proteins paraplegin, PINK1, and mitofusin 2 cause forms of HSP, Parkinson's disease, and CMT, respectively, and mutant forms of SOD1, Parkin, DJ-1, and huntingtin proteins all damage mitochondria. Finally Aβ, excitotoxic glutamate, and MPP+ all damage both mitochondria and axonal transport. Two recent studies have formally quantified the effect of mitochondrial damage on axonal transport. First, antimycin (an inhibitor of electron transport at complex III) was used to inhibit mitochondrial function; second, the effect of ALS mutant SOD1, which selectively associates with and damages mitochondria, was investigated. In both studies, damage to mitochondria resulted in a net increase in their retrograde movement (De Vos et al. 2007, Miller & Sheetz 2004). Such changes in mitochondrial dynamics predict that their numbers will be reduced in axons and that they will accumulate in cell bodies. For mutant SOD1, this prediction is upheld with the result that each remaining mitochondrion must serve an axonal segment of approximately twice the size of that in control neurons (De Vos et al. 2007). ALS-associated accumulation of mitochondria in cell bodies/axon hillocks are not restricted just to experimental systems but are also seen in human ALS cases (Sasaki & Iwata 2007). Thus not only are mitochondria damaged within mutant SOD1 axons, but also their numbers are dramatically reduced. Although mitochondrial transport and distribution have been quantified only in selected cases, some evidence shows that similar depletion of mitochondria numbers/function within axons occurs in other neurodegenerative diseases (Brownlees et al. 2002, Stamer et al. 2002). Also, mitochondria are a target for damage by Aβ in Alzheimer's disease, and Aβ disrupts mitochondrial transport (Manczak et al. 2006, Rui et al. 2006). Therefore, one possibility is that mitochondria represent one of the principal targets for age-related injury in at least some neurodegenerative diseases. The key role of mitochondria as suppliers

of ATP fuel for molecular motors implies that any damage to these organelles and/or related defects in their distribution will likely have a profound effect on axonal transport and, as a consequence, axonal maintenance and function (**Figure 4**).

SUMMARY POINTS

1. Defects in axonal transport are early pathogenic events in a number of human neurodegenerative diseases.
2. Disruption to axonal transport can occur via a number of routes. These disruptions include damage to (*a*) molecular motors, (*b*) microtubules, (*c*) cargoes (such as inhibiting their attachment to motors), and (*d*) mitochondria, which supply energy for molecular motors.
3. Age-related damage to mitochondria may amplify any primary defects to axonal transport. In this way, disruption to mitochondria may explain why many neurodegenerative diseases are diseases of old age.

FUTURE ISSUES

1. Which mechanisms regulate anterograde vs. retrograde transport of disease-associated cargoes?
2. Which mechanisms control attachment of disease-associated cargoes to kinesins and dynein? In particular, what role does phosphorylation of kinesins and dynein play in cargo binding, and how is this phosphorylation regulated?
3. Which mechanisms control mitochondrial transport? How does damage to mitochondria inhibit anterograde transport?

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

Work in the authors' laboratories is supported by grants from the MRC, Wellcome Trust, MNDA, BBSRC, European Union 6th Framework NeuroNE Network of Excellence, ART, and Alzheimer's Association. We apologize that, owing to space restrictions, we were unable to directly cite many of the important contributions that have been made to this field.

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Annual Review of Neuroscience

Volume 31, 2008

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