Published in final edited form as:

Prog Neurobiol. 2012 December ; 99(3): . doi:10.1016/j.pneurobio.2012.03.006.

Axonal transport and neurodegenerative disease: Can we see the elephant?

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Abstract

Although it is well established that axonal transport defects are part of the initiation or progression of some neurodegenerative diseases, the precise role of these defects in disease development is poorly understood. Thus, in this article, rather than enumerate the already well-reviewed evidence that there are transport deficits in disease, I will focus on a discussion of two crucial and unanswered questions about the possible role of axonal transport defects in HD and AD. (1) Are alterations in axonal transport caused by changes in the normal function of proteins mutated or altered in HD and AD and/or do such alterations in transport occur as a result of the formation of toxic aggregates of peptides or proteins? (2) Do alterations in axonal transport contribute to the causes of HD and AD or are they early, or late, secondary consequences of other cellular defects caused by disease-induction?

Keywords

Alzheimer's disease; Huntington's disease; Axonal transport; Kinesin; Dynein

Axonal transport is essential for the movement of vital proteins, vesicles, organelles, signaling molecules, and other materials to the axon, and between cell body and synapse. Substantial evidence establishes the likely role of axonal transport defects in neurodegenerative diseases such as Huntington's Disease (HD), Alzheimer's Disease (AD), and perhaps other neurodegenerative diseases (Caviston and Holzbaur, 2009; Chevalier-Larsen and Holzbaur, 2006; De Vos et al., 2008; Duncan and Goldstein, 2006; Goldstein, 2003; Gunawardena and Goldstein, 2005; Morfini et al., 2002, 2005, 2009a; Muresan and Muresan, 2009; Stokin and Goldstein, 2006). Initial evidence for this supposition came from neuropathology observations of disruptions in microtubule arrangement and dystrophic neurites, which exhibit morphological features indicative of transport defects (e.g., (Terry, 1998)). These changes were initially interpreted as being secondary to mutations or other environmental insults leading to toxic aggregated or oligomerized A β or tau species in neurofibrillary tangles (NFTs) in AD, or to the formation of toxic polyglutamine aggregates generated by huntingtin mutations that cause HD. However, as discussed below, numerous studies have reported that mutations in genes implicated in neurodegenerative disease, or expression of proteins implicated in disease, can cause changes/reductions in rates and

character of axonal transport. Finally, the discovery that mutations in genes encoding motor proteins or motor protein regulatory factors can cause neurodegeneration, e.g., in Hereditary Spastic Paraplegia and motor neuron disease (Puls et al., 2003; Reid et al., 2002), point in the same direction. Thus, there are strong arguments in favor of the idea that defects in axonal transport can contribute to at least some neurodegenerative diseases.

1. Are alterations in axonal transport caused by changes in the normal function of proteins mutated or altered in HD and AD?

HD is caused by mutations in the huntingtin gene that encode an expansion of a polyglutamine repeat in the huntingtin protein. The expansion of polyglutamine repeats in huntingtin appears to cause both malfunction and aggregation of the huntingtin protein. Rare hereditary, i.e., familial forms of AD, are caused by mutations in the presenilin genes, or the amyloid precursor protein (APP) gene. These mutations lead to changes in proteolytic processing of APP such that elevated levels of potentially toxic A β species are produced. AD can also be sporadic in which case a number of genetic risk factors appear to interact with environmental factors to cause disease, perhaps also by elevating toxic A β peptides. Considerable evidence suggests that transport defects can be caused by HD and AD associated mutations and are the result of reduction or alteration of the normal function of the gene products in axonal transport. But, there is also evidence that peptide or protein aggregation may also contribute to failures of axonal transport in disease. Thus, both points of view may be correct.

For example, in the case of poly-glutamine expansion mutations that cause HD, alterations in transport have been reported in cases where poly-glutamine expansion mutations are introduced into the endogenous huntingtin locus with consequently normal endogenous levels of expression (Gauthier et al., 2004; Her and Goldstein, 2008; Trushina et al., 2004). Axonal transport phenotypes are also induced when poly-glutamine expansion mutations in huntingtin are overexpressed (Anne et al., 2007; Caviston and Holzbaur, 2009; Colin et al., 2008; Gunawardena et al., 2003; Her and Goldstein, 2008; Morfini et al., 2006, 2009b; Szebenyi et al., 2003; Trushina et al., 2004). Finally, loss of huntingtin function also leads to axonal transport deficits (e.g., (Gauthier et al., 2004; Gunawardena et al., 2003)). When combined with biochemical evidence that huntingtin directly and indirectly interacts with components of the transport machinery (Engelender et al., 1997; Gauthier et al., 2004; Li et al., 1998), and evidence in non-neuronal cells that huntingtin is required for dynein-mediated organelle positioning (Caviston et al., 2007, 2011), the reasonable conclusion is that huntingtin normally plays some role in axonal transport, although exactly what that role is has not been well established. There is a suggestion that huntingtin may play a role in the control of the direction of vesicle movement which is an interesting possibility that needs further work to validate (Colin et al., 2008; Zala et al., 2008). In all of these cases, there is strong evidence that alterations in transport caused by poly-glutamine expansion mutations in the huntingtin gene can occur in the absence of visible aggregates. Thus disease-causing mutations may induce early defects in neuronal physiology as a result of perturbation of the normal function of huntingtin in axonal transport. However, there is also evidence that aggregates can poison axonal transport by physical blockage (Gunawardena et al., 2003; Lee et al., 2004; Sinadinos et al., 2009), by titration of motor protein subunits, or by causing damage to other systems such as protein turnover, kinase activation, mitochondrial health, etc. (Morfini et al., 2006, 2009b). There is also some evidence that the severity of axonal transport poisoning by huntingtin poly-glutamine expansion mutations may vary among neuronal types, which could perhaps explain some of the regional specificity of disease (Han et al., 2010; Her and Goldstein, 2008). Taken together, these data about huntingtin lead to the conclusion that axonal transport may be inhibited both by alteration of normal huntingtin function, and also by aggregates of huntingtin or its fragments. The important unanswered

question, however, is what is the relative severity of axonal transport abnormalities caused by altered huntingtin function compared to huntingtin aggregates?

In the case of AD there are a number of suggestions for how the key proteins involved directly or indirectly in disease, i.e., APP, presenilin, BACE, and tau, interact with the transport machinery. For APP, one set of experiments suggests that APP, which is itself an abundant protein that undergoes axonal transport, may play direct roles in axonal transport (Gunawardena and Goldstein, 2001; Kamal et al., 2001, 2000; Satpute-Krishnan et al., 2006; Smith et al., 2010b; Torroja et al., 1999). For example, excess APP can poison axonal transport (Gunawardena and Goldstein, 2001; Rusu et al., 2007; Salehi et al., 2006; Smith et al., 2007, 2010a), while loss of APP induces defects in axonal transport (Gunawardena and Goldstein, 2001; Kamal et al., 2001; Smith et al., 2010b). The role of APP in axonal transport may be carried out by directly interacting with kinesin light chain in a binary complex, or indirectly in a ternary complex with a Jun-kinase scaffold protein called JIP1, which may be required for transport of APP vesicles themselves (Cottrell et al., 2005; Horiuchi et al., 2005; Inomata et al., 2003; Kamal et al., 2001, 2000; Matsuda et al., 2003; Muresan and Muresan, 2005; Satpute-Krishnan et al., 2006). In this view, poisoning of axonal transport by APP overexpression is not a result of poisoning by A β . This proposal is supported by several investigations (Gunawardena and Goldstein, 2001; Rusu et al., 2007; Salehi et al., 2006; Stokin et al., 2008). One suggestion is that this poisoning of axonal transport comes from overexpression of the C-terminus of APP, which competes for available kinesin motor or JIP1. In this regard, there is one report that claims that the interaction between kinesin light chain and APP is “non-specific” (Lazarov et al., 2005). Nonetheless, Fig. 1 of this report clearly demonstrates that there is an APP-kinesin light chain interaction, which must be relatively high affinity given the likely low concentrations of the proteins studied in the assays. Interestingly although overexpression of APP clearly causes defects in axonal transport independent of the A β region, human A β has been reported to cause axonal transport defects under some conditions, and this poisoning may be dependent upon the presence of tau protein (Calkins and Reddy, 2011; Decker et al., 2010; Hiruma et al., 2003; Kasa et al., 2000; Rui et al., 2006; Shah et al., 2009; Takashima et al., 1995; Vossel et al., 2010; Wang et al., 2010). The key unanswered question is the relative magnitude of transport defects caused by aggregated or oligomeric or other forms of A β relative to A β -independent axonal transport defects caused by alterations in APP expression and perhaps mediated by the APP C-terminus.

A second area of controversy concerns the question of whether β -secretase and gamma-secretase (presenilin) are transported into the axon, and, if they are, whether they are located in the same axonal vesicles as APP and therefore might regulate APP transport via secretase activity. Initial reports were based on biochemistry and on immunofluorescence localization (Kamal et al., 2001; Kasa et al., 2001; Papp et al., 2002; Sheng et al., 2003). Although there was skepticism about these results (Lazarov et al., 2005), more recent work confirms that BACE activity and protein and gamma-secretase activity and presenilin protein can be found in axons and thus clearly must be transported (Goldsbury et al., 2006; Nikolaev et al., 2009). Whether some or all of this transport of secretases happens in APP vesicles needs further clarification.

In this regard, it is worth noting that there are several implied assumptions in the literature, some with supporting evidence, about the sorting and trafficking pathways of APP, BACE and presenilin into the axon. Specifically, there appears to be a small amount of evidence (Nakata and Hirokawa, 2003; Simons et al., 1995) and a corresponding assumption that all axonal vesicles containing these proteins originate directly from the trans-Golgi. But, there is also evidence that raises the possibility that this simple pathway may not be used for all axonal membrane proteins including APP. Specifically, there is evidence that at least some

APP processing happens in the somatodendritic domain (cell body) but there is also evidence for and against secretion of A β from axons and substantial evidence for axonal transport of full-length and secretase processed fragments of APP, e.g., in the perforant pathway (Buxbaum et al., 1998; Lazarov et al., 2002; Muresan et al., 2009; Sannerud et al., 2011). But, if as seems likely based on work in both non-neuronal and neuronal cells, the APP processing machinery is active primarily in endosomes, then the sensible conclusion is that APP fragments that enter the axon could be generated in an endosomal compartment (Muresan and Muresan, 2006). This view implies that there may be a second route via endosomes, and endosome derived vesicles, into the axon for APP, APP fragments, and perhaps the processing machinery (Carey et al., 2005; Evin et al., 2010; Kaether et al., 2006; Koo and Squazzo, 1994). In this context, polarized epithelia are known to have multiple trafficking pathways for membrane proteins to go from trans-Golgi to apical or basolateral membrane domains (Weisz and Rodriguez-Boulant, 2009). Strikingly, only a subset of these proteins go directly from the trans-Golgi to the membrane; many are routed through one of a variety of endocytic compartments. One of these pathways, transcytosis, uses an intermediate endosomal compartment to sort traffic that goes from the TGN to the basolateral surface and then proceeds to the apical surface via an endosome. In this context, there is evidence that some neuronal proteins such as NCAM and TrkA may use a transcytosis pathway to go from the TGN to the axon (Lisiecka and Winckler, 2011). In view of the reported complexity of APP processing and sorting, and given the finding that APP and TrkA may in some cases be present in the same axonal vesicles (Kamal et al., 2001), these observations lead to the testable suggestion that APP might be routed to the axon by a combination of direct and/or indirect mechanisms via the endosome. Secretases may also undergo comparably complex pathways of sorting and trafficking to the axon (Sannerud et al., 2011).

Interestingly, in the context of sorting and trafficking pathways, presenilin has been suggested to play a role in vesicle trafficking and axonal transport. Presenilin mutations or mutant transgenes have been reported to inhibit anterograde axonal transport, and to reduce the amount of full-length APP entering axons (Cai et al., 2003; Lazarov et al., 2007; Pigino et al., 2003; Stokin et al., 2008). To what extent presenilin alters APP trafficking through protease activity to generate different APP fragments including A β , or exerted through non-protease dependent pathways, is unclear as is the relative magnitude of such effects. In this regard, over-expression of BACE leads to increased β -cleavage in the somatodendritic domain and consequent reduced axonal entry of full-length APP (Lee et al., 2005).

2. Are transport alterations causative or secondary to other cellular defects caused by disease-induction?

In HD, dystrophic neurites can be found both relatively early and late in disease, suggesting that axonal transport failures may occur both early and late in the course of disease (Sapp et al., 1999). More to the point is evidence that overexpression of poly-Q expansion mutations in the huntingtin gene, or introduction of poly-Q expansion mutations into the endogenous huntingtin gene, can cause transport defects in the absence of other obvious pathologies (Caviston and Holzbaur, 2009; Colin et al., 2008; Gauthier et al., 2004; Gunawardena et al., 2003; Han et al., 2010; Her and Goldstein, 2008; Morfini et al., 2009b; Szebenyi et al., 2003; Trushina et al., 2004; Twelvetrees et al., 2010; Zala et al., 2008). Thus, if early dystrophic neurites, or defects in the absence of aggregates, signify primary defects, and late dystrophic neurites signify secondary effects, these types of data suggest that HD mutations could, but not necessarily must, cause both early primary and late secondary deficits in axonal transport in mutant neurons.

In the case of AD, there is strong evidence for both early and late transport defects. Evidence for late defects comes from observations of dystrophic neurites including axonal dystrophy, microtubule destruction, and the aggregation of tau protein, a microtubule regulator and motor regulator, into neurofibrillary tangles (Mandelkow et al., 2003; Morfini et al., 2002, 2009a; Stokin and Goldstein, 2006; Terry, 1998). Evidence for early defects comes from observation of axonal dystrophy/axonal blockages in postmortem samples from early sporadic AD, and from the observation in model systems that excess APP, or presenilin mutations, can cause early defects in axonal transport in the absence of other obvious pathologies (Lazarov et al., 2007; Pigino et al., 2003; Stokin et al., 2008, 2005). Strikingly, these same genetic lesions are reported to cause trafficking defects in the endosomal/lysosomal pathways in human fibroblasts, mouse neurons, and human neurons (Israel et al., 2012; Qiang et al., 2011). Such trafficking problems could cause axonal transport defects or be a consequence of cell body transport defects (Jiang et al., 2010; Lee et al., 2010, 2011; Salehi et al., 2006). In the former case, alterations in motor loading and regulation prior to axonal entry could be secondary to alterations in endosomal maturation, character, or perhaps size control. In the latter case, motor loading or regulation on endocytic vesicles and intermediates in neuronal cell bodies could be abnormal, leading to changes in kinetics, maturation rates and trafficking of endocytic cargoes. The recent finding of GWAS hits in and around genes that may play important roles in endocytosis and trafficking, e.g., SORL1 and PICALM, raises the possibility that these ideas may be applicable to sporadic AD in addition to familial AD (Bertram et al., 2010).

3. Conclusions

There is a great deal of experimental data that supports the hypothesis that axonal transport defects in HD and familial AD are primary defects caused by mutation-induced changes in normal protein functions, by toxicity induced by oligomerization or aggregation, and that these defects can be both early in disease, i.e., primary defects and late in disease where they may possibly be secondary to unrelated abnormalities. Similar arguments may be valid for sporadic AD, though with less evidence to support them. Importantly, it is not possible based on available evidence to rigorously draw any conclusions about the relative extent of primary effects on axonal transport of disease-causing mutations versus secondary effects of insults to cellular processes such as transcription, vesicle and organelle behavior, protein turnover, and synaptic alterations. Similarly, it is not possible to evaluate the relative significance of transport changes in neuronal function relative to the other alterations reported. For both issues, a persistent obstacle to rigorous comparative evaluation is the sheer diversity of systems and approaches used to evaluate the effects of HD and AD mutations on axonal transport. Thus work reported has used fixed and live cells derived from *Drosophila*, mouse, squid, worms, and humans, and also has included *ex vivo* squid axoplasm, biochemistry, many types of *in vivo* neurons (retinal, forebrain cholinergic, perforant pathway, sciatic nerve), cultured neurons of many different types (hippocampal, cortical, striatal, peripheral sensory), pseudo-neurons in culture (e.g., PC12 cells), and non-neuronal cells. In fact, a recent direct comparison of several mouse models of AD revealed considerable phenotypic diversity (Li et al., 2011). While this breadth of approaches is very useful for uncovering shared cellular principles basic to many systems, it has failed to reveal the relative magnitude of effects, which may in fact differ across systems and neuronal types and will certainly differ when comparing non-neuronal cells to highly polarized mature neurons.

Moving forward there are two key avenues that must be pursued to resolve these issues. First, it would be desirable for investigations of phenotypes caused by HD and AD mutations to be pursued in live bona fide mouse or human neurons (e.g., (Israel et al., 2012; Qiang et al., 2011)) in which multiple phenotypes can be evaluated in the same cells

to allow rigorous comparison of timing, relative magnitudes of phenotypic defects, cause and effect relationships, and the induction of pathological phenotypes. Second, while considerable information has been gleaned from analysis of fixed material, rigorous and thorough investigation of the dynamics of trafficking and movement, and pathological inducers, in living neurons will be critical to gain a deeper understanding of these issues. Perhaps the best analogy to describe our current situation is the Indian parable of the three blind men and the elephant, each of which only feels the tail, leg, or trunk (http://en.wikipedia.org/wiki/Blind_men_and_an_elephant). We are clearly seeing the pieces, but it is time to do experiments that will help us see the whole elephant.

Acknowledgments

I apologize to the many authors whose work I could not cite in this short article owing to space considerations. The development of ideas described in this article was supported by grants from CIRM and NIH. I am an Investigator of the Howard Hughes Medical Institute.

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Abbreviations

HD	Huntington's Disease
AD	Alzheimer's Disease
APP	amyloid precursor protein
TGN	trans-golgi network
BACE	beta-secretase