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What is the Link Between Protein Aggregation and Interneuronal Lesion Propagation in Neurodegenerative Disease?

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1. Introduction

During the past 10-15 years it has become clear that most major neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, ALS, tauopathies, prion diseases and trinucleotide repeat diseases – henceforth to be referred to collectively as AANDs) share cellular and systemic features that suggest a common underlying mechanism of pathogenesis. At the cellular level, our understanding of the common aspects of AAND pathogenesis can be most simply summarized in terms of the downstream consequences of uncontrollable protein oligomerization and aggregation in postmitotic cells. The aggregated proteins block or disrupt normal proteosomal turnover and autophagy and become abnormally modified over time, generating toxicity via multiple pathways (mitochondrial damage, increased intracellular Ca++, caspase activation etc.) eventually leading to neurodegeneration and neuron death. This hypothesis is consistent with a key genetic similarity between these diseases – e.g. that familial forms are typically caused by autosomal dominant mutations that favor aggregation (in the case of asyn, tau, PrP and SOD1) or formation (in the case of APP and CAG repeat sequences) of disease-specific, aggregation-prone proteins. These similarities have suggested to many that a single central defect (i.e. the failure of normal protein folding) lies at the heart of most or all of the diseases listed above, and has led to them being categorized be some as "protein misfolding diseases".

While the importance of aggregate formation (and its attendant cellular dysfunctions) in each of these diseases is well established and has been intensively studied, our understanding of the intercellular and systemic aspects of these diseases is less detailed. That said, enough has been learned about their roles in neuronal biology and pathobiology and in the neuropathogenesis of AANDs to generate a general consensus that AAND development is 1) not cell autonomous and 2) that AANDs have another common hallmark– the progressive involvement of synaptically connected regions of the CNS over time in disease-specific patterns. Furthermore, it has become clear that important synergistic interactions between specific aggregation-prone proteins (tau and asyn (83), PrP and APP/Abeta (134), PrP and tau (216), PrP and asyn (95) may occur at both at the cellular and interneuronal level that affect the pathogenesis of specific AANDs. However, while neurofibrillary lesions develop according to characteristic, disease-specific sequences between highly interconnected regions of the brain in some AANDs (e.g. AD, tauopathies

and LBD), the mechanisms by which the tendency toward aggregate formation is propagated between neurons as the disease progresses remains unclear, as does the degree to which such mechanisms contribute to disease pathogenesis as a whole. Similarly, there is still a gap between what we now know about the normal (mostly as monomer) and toxic (mostly as oligomers and aggregates) functions of each of these proteins at the cellular level. We know a good deal about the factors that favor AAND oligomerization, but very little about how oligomerization actually occurs in human disease. In particular, we have no real idea how these factors might 1) interact synergistically to drive cytotoxicity and degeneration and 2) are related to the mechanisms by which interneuronal toxicity is propagated between neurons in different parts of the brain. This review will attempt to integrate relatively recent findings about the interactions between the 3 most widely studied of these proteins (i.e. tau, alpha synuclein and the prion protein) both with each other and with cellular mechanisms associated with unconventional protein secretion into a framework that will account for common pathogenic features of these diseases and suggest future avenues of inquiry. For the sake of clarity, the discussion will be focused on asyn, tau and PrP and their interactions with APP/Abeta, and will omit a detailed consideration of other diseases that may have similar pathogenetic features (e.g ALS, Huntington's disease) and associated aggregation-prone proteins (SOD1, polyglutamine expansions, TDP-43, FUS), except when these become relevant to the discussion of general mechanisms. It will be guided by the example of PrP misprocessing and prion diseases, where the key link between intracellular protein aggregation, interneuronal transfer and the spread of neurofibrillary lesions through the brain has already been definitively established and which provides hints as to where to look for similar links in other AANDs.

Overview of common neuropathological and genetic aspects of AAND pathogenesis at the cellular and systemic levels

The predominant focus of basic research over the past 2 decades into the pathogenesis of all of the major AANDs has been on 1) the mechanisms responsible for protein aggregate formation and 2) the nature of cytotoxic changes that accompany and result from the aggregation of each of the proteins being discussed. As a consequence, aggregation-associated events and downstream consequences of aggregation such as the failure of protein turnover mechanisms in long-lived postmitotic cells such as neurons are among the best-characterized cytopathological features of neurodegenerative diseases. This work has generated a broad consensus that aggregation causes the failure of normal protein turnover mechanisms and the consequent development of abnormal toxic routes of protein disposal are central pathogenic events of the degenerative diseases that afflict the human central nervous system as it ages. Common toxic elements downstream of protein aggregation in AANDs include: 1) aggregation associated damage to protein turnover mechanisms, 2) mitochondrial dysfunction and or maldistribution leading to apoptosis-associated changes due to low ATP, generation of oxidative stress and abnormal Ca++ fluxes and 3) aggregate-mediated sequestration of normal proteins resulting in a loss of the normal function associated with sequestered proteins.

The classic example of a neuropathogenesis pattern suggestive of lesion spread in AANDs (outside of prion diseases) is provided by Alzheimer's Disease (AD). Ever since the seminal studies of Heiko and Eva Braak (27), it has been apparent that the neurofibrillary degenerative changes of AD develop in a characteristic sequence that closely follows the clinical progression of symptoms (11, 203). The earliest changes occur in specific limbic

regions concerned with olfaction, spatial localization and episodic memory formation and consolidation (transentorhinal, entorhinal, pyriform cortices), functions that are typically compromised in the earliest clinical (and even preclinical) phases of AD. This is followed by the progressive involvement of limbic and paralimbic centers including the hippocampus, adjacent allocortical regions of the medial temporal lobe (e.g. subiculum), the insula and anterior cingulate cortex. Again, these neuropathological changes match the development of AD symptoms quite closely, with changes in emotional processing and short term memory becoming evident by the time AD can be recognized as such in the clinic, together with the onset of cognitive changes. The most prominently affected limbic centers are strongly interconnected with one another synaptically as well as functionally (203), as would be necessary for lesion propagaion via transsynaptic toxicity transfer. The areas affected in this "limbic stage" of mild AD make up only a small proportion of the brain by volume (24), but make and receive major inputs to and from large neocortical regions that become involved in later (isocortical) stages of AD, which could account for the sudden expansion of AD neurofibrillary lesions at the onset of Braak Stage 5 (24, 202). Although some regions of the brain (e.g. the primary sensory and motor cortices) are almost never involved significantly in AD despite being strongly interconnected with highly vulnerable limbic centers, it seems likely that this is due to cell specific or even connectivity-specific factors (8) that may delineate individual AANDs from one another (63, 59, 109, 116).

The progressive involvement of synaptically interconnected brain regions seen in AD is mirrored in non-AD tauopathies such as frontotemporal dementia (FTD), Pick's Disease (PiD) progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) and involve some of the same parts of the brain (prefrontal/frontal cortex temporal cortex, insula) although the areas of initial involvement are different from AD and from each other (9, 10, 11, 63). Similarly, Parkinson's Disease (PD) and PD-associated dementing syndromes such as Lewy Body Disease (LBD) share a common set of vulnerable loci (dopaminergic neurons in the substantia nigra, brainstem autonomic nuclei, olfactory bulb and neocortical loci) but vary significantly in the initial nidus of vulnerability and the degree of involvement of other parts of the brain (48, recently reviewed in 3, 50, 59). Also, the progression of Lewy Body containing lesions in LBD and PD differs significantly from that seen in AD in that it is not tightly linked to overall clinical or neuropathological severity (28). Overall, significant overlap between the areas vulnerable to synucleinopathies with those involved in early stages of AD (nucleus of Meynert, olfactory bulb, various isocortical loci) and in non-AD tauopathies (basal ganglia, isocortex). Familial prion diseases (fatal familial insomnia, Creutzfeld Jacob disease (CJD), Gerstmann-Schenker-Straussler syndrome) show a similar pattern (lesion evolution via a subset of synaptically connected areas from characteristic initiation loci) with a common set of vulnerable loci (thalamus, neocortex, ANS, cerebellum) that partly overlaps those of the other ANDDs (illustrated in Figure 1).

Another distinctive feature of AANDs as a group is the manifestation of each syndrome in both sporadic and familial forms, with exonic or intronic mutations in a specific aggregation-prone protein being sufficient to generate a (usually) dominant allele capable of replicating all aspects of the (usually more common) sporadic disease with high penetrance (197). Perhaps the most interesting aspects of this pattern are a) the degree of similarity between sporadic and familial disease forms, and b) the greater tendency of sporadic, but not familial, disease forms to show asymmetrical development, especially in non AD tauopathies (59, 143). These emphasize the importance of both selective vulnerability and synaptic connectivity as common factors in these diseases, and is consistent with the

intriguing relationship between acquired, sporadic and familial forms of prion diseases such as Creutzfeld-Jacob disease (CJD), where the point of origin is clearly different in each case, but common aspects of vulnerability and synaptic connectivity are sufficient to generate a common clinical presentation (CJD), despite the presence of characteristic differences in lesion form (175). A similar relationship may hold between certain non-AD tauopathies and clinically identical diseases (both called FTDP or FTDP-17) involving loss of function changes in RNA-binding proteins (TDP-43, progranin) involved in the localization and translation of cytoskeletal proteins (hnnRPs), including tau and neurofilament proteins (147). Here, TDP-43 and or progranin may be activating downstream elements of a common

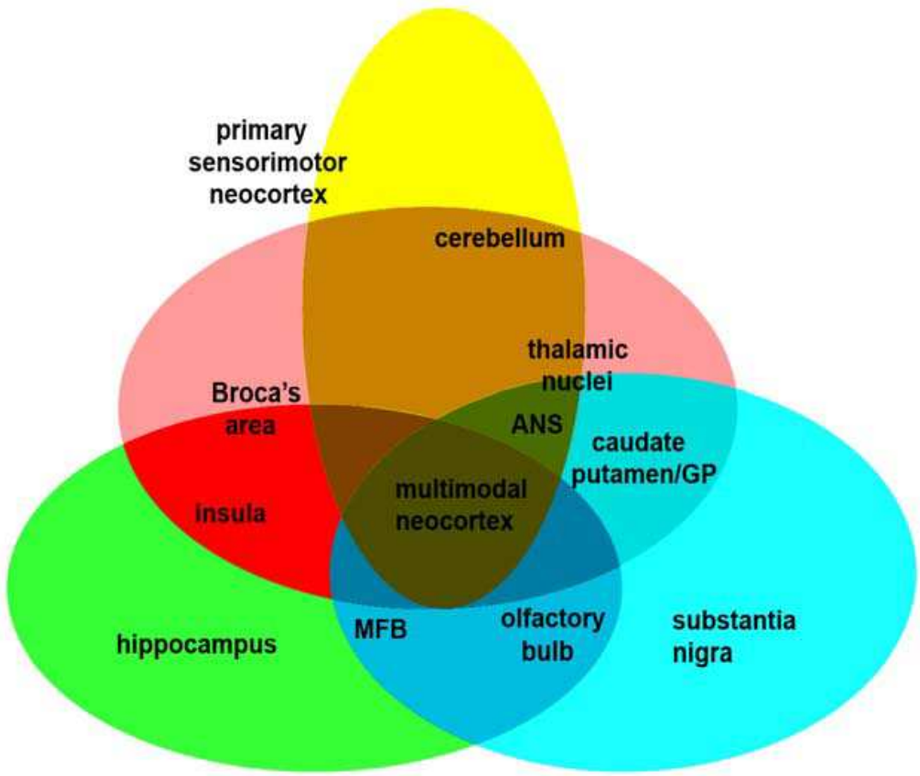

Fig. 1. Schematic illustrating the relationship between the characteristically vulnerable regions in AD, (green) nonAD tauopathies (pink), familial prion diseases (yellow) and synucleinopathies (blue). Regions typically involved in multiple AAND disease classes are shown in overlapping areas. Individual syndromes from all of these diseases eventually involve polymodal (associative) isocortical areas and thus cause dementia, even though severe cognitive changes may be absent or develop very late in other members of each group (e.g. Parkinson's Disease, fatal familial insomnia). Vulnerable areas in familial and sporadic forms of each AAND are identical, with familial syndromes beginning earlier and progressing faster than sporadic ones. Characteristic areas of vulnerability for frontotemporal syndromes (FTDP-U) that involve TDP-43 and FUS rather than tau aggregates and acquired forms of prion disease (vCJD, kuru) are virtually identical to non AD tauopathies (pink) and familial prion diseases (yellow), respectively, possibly owing to the presence of "prion like" motifs in these proteins (53). ANS: autonomic nervous sytem, MFB: medial forebrain bundle/nucleus of Meynert, GP: globus pallidus

misprocessing pathway that can also lead to the spread of tau–based lesions in the same overall pattern, rather than recruiting tau directly. Such a pathway might involve the mislocalization of proteins important in the maintenance of neuronal polarity from the axon to the soma and dendrites via a failure of hnnRP-mediated mRNA localization. This possibility is particularly intriguing since a) hnnRP interactions with the 3′ UTR of the mRNA encoding tau have been shown to be responsible for both tau localization to the axon (12, 146) and the generation of neuronal polarity (147) and b) the neuropathology of AD and non-AD tauopathies suggests that polarity loss plays a role in tauopathy pathogenesis (107, 1741). Overall, the common neuropathological and genetic features of AANDs involving tau, asyn and PrP are largely consistent with the existence of a common lesion propagation mechanism (or several closely related mechanisms) that involves direct interneuronal transfer of a toxic factor between adjacent and transsynaptic neurons.

Linking aggregation to lesion spreading – The case of the prion protein

The prototypic (and most extreme) example of an aggregation-prone protein that propagates its misfolded state at the protein, cellular and even organismal level is of course the prion protein (PrP), the misfolding of which mediates a class of mostly rare neurological degenerative diseases (transmissable spongiform encephalopathies) of humans and other mammals, the best known of which are CJD, scrapie, and kuru. Due to the pioneering work of Tikva Alper, Carlton Gadjusek and (particularly and most recently) Stanley Prusiner and co-workers over the past 50 years, and after rigorous verification by often highly skeptical investigators, there is now a general consensus that the so called "Prion hypothesis" proposed by Prusiner 30 years ago has correctly predicted key peculiarities of prion disease transmission such as the effect of PrP knockouts (31) and thus correctly describes the pathogenesis of these diseases (reviewed in 3, 49, 175). The Prion Hypothesis states that individual molecules of a single, widely expressed protein (the prion protein, or PrP) becomes misfolded and misprocessed in a manner that makes it adopt a neurotoxic conformation (PrP^{Sc}), but more importantly, permits it to transmit this conformation on to other prion proteins in the normal (PrP^{C}) conformation. The peculiar and controversial history of prion biology thus provides us with a highly verified example of how the misprocessing of an aggregation-prone protein into a toxic form can result in the interneuronal propagation of a protein with self regenerating, neurotoxic characteristics, and thus effect the spreading of neurofibrillary lesions to adjacent, presynaptic or postsynaptic neurons. The likely relevance of PrP misprocessing mechanisms to the pathogenesis of tauopathies, synucleinopathies, and other AANDs is further underscored by recent demonstrations that immensely subtle differences in PrP misprocessing and PrP^{Sc} structure appear to mediate the distinctive clinical and neuropathological manifestations of the various prion diseases (18, 40, 49, 168). In addition, recent studies of the normal cellular functions of PrP^{C} suggest that it is involved in the function of the actin-rich subcortical cytoskeleton and its interactions with microtubules, cellular membrane trafficking, cell adhesion and signal transduction in a variety of cell types (reviewed in 3, 53). In neurons, PrP^{C} appears to play a critical (if subtle) role in synaptic plasticity and most interestingly, in the propagation of HIV infection in the CNS (149, 180). The similarities in the cellular function, localization and misprocessing of PrP, APP/Abeta, asyn and tau identify likely points of interaction between these proteins, and synergy in their misprocessing, which are discussed futher below.

		APP/Abeta (AD, DS)	tau (PiD, PSP, CBD)	Asyn (PD, LBD)	PrP^{Sc} (CJD, GSS, FFI, kuru, vCJD)
Etiology	Sporadic	Most (80%)	Varies	Most (95%)	Probably most (CJD)
	Dominant	APP (1%) PS1, PS2	tau (exonic, isoform splicing)	Asyn LRRK2	PrP
	Recessive	–	–	DJ1, Pink1, Parkin	–
Risk Factors	Genetic	APP expression (DS) APoE4 isoform	tau expression (H1 haplotype)	diverse loci in mitochondria	PrP129
	Environmental	TBI, axotomy	TBI, axotomy	ROS-generating toxins	PrP^{Sc} in diet, iatrogenic risk
Neuropathology					
	Neuronal vulnerability factors	plasticity large size glutamatergic	3R/4R isoforms tau expression NF expression	dopaminergic High ROS	varies with mutation (FFI/CJD/GSS) Cerebellum (kuru, vCJD)
	Neuritic Sprouting	dystrophic neurites neuropil threads	neuropil threads	dystrophic neurites	dystrophic neurites
	Connectivity-based pathogenesis	yes	yes	yes	yes
Propagation	Clinical	no	no	yes	yes
Interneuronal transfer (human protein)	secretion	in situ culture	in situ culture	culture	culture
	secretion mechanism	exosome	exosome*	exosome	exosome
	uptake	culture	in situ culture	culture	in situ
	transmission	in situ (IP injection)	in situ	in situ	in situ
	transmitted toxicity	in situ (tangles) culture	in situ culture	culture	in situ culture
Synergy	Clinical	PD, LBD	PD, LBD	AD, tauopathy	Unclear
	Neuropathology	PD, LBD (tau)	Asyn Abeta	tau, Abeta	tau, Abeta
	Protein interaction	Asyn PrP tau (binding)	Asyn (coaggregation) PrP (binding) APP (binding)	tau (coaggregation) Abeta PrP	Asyn Abeta tau

Table 1. Comparison of the pathobiological characteristics of 4 aggregation-prone proteins responsible for most aggregation-associated neurodegenerative diseases (AANDs) in humans The table summarizes aspects of disease-associated misprocessing of 4 aggregation-prone proteins (amyloid precursor protein/beta amyloid (APP/Abeta) tau, alpha synuclein (asyn) and prion (PrP)) discussed in the text that are relevant to both aggregate formation and lesion propagation in major human neurodegenerative diseases (Alzheimer's Disease (AD) Down's Syndrome (DS), Pick's Disease (PiD), progressive supernuclear palsy (PSP), corticobasal degeneration (CBD), Parkinson's disease (PD), Lewy Body disease (LBD), Creutzfeld-Jakob disease (CJD), Gerstmann Straussler Schenker disease (GSS), fatal familial insomnia (FFI), kuru and variant CJD (vCJD). *publication in review (185)

2. Common structural/functional features of AAND proteins favoring aggregation and intercellular transfer

General molecular and cellular considerations

The abnormal and irreversible oligomerization and/or aggregation of specific proteins (e.g. tau, asyn, PrP) is the central common feature in AAND cytopathogenesis and by itself accounts for many of the other common cellular features of these diseases (a good review of the subject can be found in 196). Familial AANDs are typically induced by intronic, autosomal dominant mutations that either directly favor aggregation (tau, asyn, PrP), favor events that lead to generation of the aggregation-prone form of the protein (e.g. cleavage, abnormal association with other proteins, abnormal glycosylation or phosphorylation), or both (tau, PrP) (3, 50, 202). Exceptions to the autosomal dominant pattern include recessive mutations responsible for loss of function effects in protein turnover pathways (e,g, parkin 126). These genetics suggest that AAND pathology is due to a gain of function leading to aggregate formation and downstream toxicity involving the poisoning or overloading of proteasomal or autophagy-based protein turnover. A common structural feature among these proteins relevant to their tendency to aggregate is the co-existence in each one of a "core" domain which can form beta sheet interactions plus at least one other domain that inhibits this tendency, resulting in a balance between a normal conformation (rich in alpha helix or "random coil") conformation and an abnormal beta sheet-rich conformation that favors aggregation (50, 5, 156). Key common features in the cellular functions of tau, asyn and PrP include interaction with both chaperone proteins and with signal transduction elements, which might be expected of proteins capable of both aggregation and transcellular movement, respectively. Moreover, all three proteins are frequently associated with cellular membranes under normal conditions, especially in synapses (29, 71, 76, 148, 212, 213, 233) where they interact with APP (an integral membrane protein) and/or Abeta (93, 171), and are substrates for lipid raft-associated Srk family tyrosine kinases (e.g. fyn - 95, 137, 188, syk - 136 and abl - 37). In particular, the luminal localization of each protein in endosomes and/or trafficking vesicles associated with unconventional secretion (35, 78, 140, 142), reviewed in 215), and the interactions (in some cases copolymerization) that can occur between them (83, 134, 171, 216, 217) make endosomal pathways a highly plausible candidate site that might mediate the synergistic misprocessing of these proteins. An endosome-mediated common misprocessing pathway is also consistent with the availability of templating polyanionic ligands such as membrane-associated proteoglycans favoring further aggregation and toxicity (51, 52, 91, 106, 111), and the ready diversion of endocytosed proteins to unconventional secretion pathways (68, 70, 733, 102, 116, 124, 140, 175, 215).

Tau, asyn and PrP are all "switch" proteins that alternate between 2 states based on regulated charge/charge modifications. Under normal circumstances, asyn, tau and PrP function as soluble monomers that interact extensively with other proteins in the both in the cytosol and in association with cellular membranes. Soluble PrP^{C} and asyn contain alpha helical and random coil domains, and take up a predominantly random coil conformation in aqueous solution (186, 219, 231). In cells, tau normally extends along microtubules, where it stabilizes them by preventing classic dynamic instability via binding to them at multiple sites in its aggregation prone-microtubule binding domain (MTBR) (33). Tau:MT binding is itself dynamic (186), and tau interacts with fyn kinase, actin and protein chaperones via loci

that overlap the MTBR when not bound to MTs (95, 107, 189). Monomeric asyn exists in both membrane-associated and cytosolic loci, and like tau, can bind to both actin and tubulin (4). As with tau, disease-causing mutations in asyn cause it to preferentially bind to membrane-associated proteins (69). Both membrane and MT-associated asyn have been found to aggregate (4, 139), in some cases forming clusters of microvesicles (195). PrP possesses an aggregation-prone domain (octopeptide repeat) that appears to be oligomerized reversibly during endocytosis. Unlike tau, it also possesses a separate N terminal MT-binding domain (231). All three proteins possess-aggregation-prone domains via which they aggregate resulting in a significant increase in beta sheet structure (156, 187, 231). Deletion analyses of all three proteins show that the removal or inactivation of non-aggregating domains (the N terminus of PrP, the tau N and C termini, the asyn C terminus) may tip this balance toward aggregate formation (1, 38, 112, 226). Post-translational regulation of each protein via phosphorylation may also do this (5, 41, 42, 80), either because it blocks the binding of the aggregation-prone domain to its normal cellular ligand, thereby permitting self assembly (156), or by favoring conversion of soluble oligomer to insoluble higher-order aggregates (187). Familial disease mutations may mimic these changes (13, 66, 80) as well. Overall, while tau, asyn and PrP are capable of aggregate formation and normally interact with both MTs and membrane associated components, the details of how oligomer formation and membrane association is related to normal function vary considerably. A key common feature relevant to the appearance of gain-of-function properties leading to interneuronal propagation in AANDs is the existence of self-binding/assembly capable and assembly-inhibiting domains in each protein that are normally balanced in favor of monomeric functions. This can thus act as a "switch" between normal and abnormal processing pathways which may be mutated to favor oligomer formation in familial AANDs, or alternatively, be "flipped" by derangement of regulatory elements (e.g. kinase/phosphatase and protease activities) that induce these posttranslational processing events in sporadic AAND pathogenesis.

Protein misprocessing in AANDs becomes irreversible and opens processing pathways associated with cellular membranes. A key feature of almost all AANDs involving tau, asyn and PrP is that they can occur as both familial and sporadic syndromes, which suggests that a common AAND pathogenesis mechanism must involve self-regenerating alteration in cellular function that is largely irreversible. Initial stages of oligomerization (e.g. dimerization) are most likely insufficient to do this, since all 3 proteins are normally found in a variety of reversible folding states, including low level oligomers, and are ligands for membrane-associated signal transduction kinases that reversibly oligomerize downstream elements (205). However, the binding of these proteins to templating ligands is likely to create higher-order oligomers that could become subject to irreversible structural changes such as proteolytic cleavage (90, 226, 234) and covalent crosslinking (62, 118, 161, 192). The nature of ligands shown to be capable of doing this currently includes 1) the proteins themselves, in the case of PrP^{Sc} (175) and mutant asyn (227), 2) polyanions such as heparan sulfate proteoglycans (HSPGs) (106, 225) or RNA (57, 119) and 3) other aggregation-prone proteins (83, 93, 95, 216). Other effectively irreversible changes in the cellular environment may be produced by downstream toxic effects of the initial aggregates, such as protease activation (7, 169), possibly aided by ionophore formation (39, 84, 133), or the recruitment of monomers into existing toxic aggregates via sequestration (6, 120). Endocytosed proteins that bind to the membrane via charge-charge interactions will undergo an acidification of

their environment that may favor templating interactions and oligomer formation (67) Hyperphosphorylation, cleavage and aggregation of wild type tau isoforms can be induced simply by increasing the concentration of protein that is not MT-associated and thus vulnerable to misfolding (reviewed by 13, 203), causing the release of tau to the cytosol. This kind of release likely accompanies Abeta or axotomy-induced MT loss (32, 101), and thus could account for some of the dependence of tau misprocessing on Abeta generation and traumatic head injury in AD (151, 178).

While aggregate formation is a central event in the misprocessing of aggregation-prone proteins that drive AAND pathogenesis, it remains unclear how it is connected to the diversion of these proteins into the unconventional secretion pathways that might account for the interneuronal transmission of neurofibrillary lesions that appears to occur in these diseases. One possibly relevant property common to tau, asyn and PrP is their tendency to associate with membranes (29, 40, 53, 67, 173, 230, 233) and bind to membrane associated molecules such as HSPGs and fatty acids (44, 222, 225, 232). HSPG binding favors oligomer and fibril formation (52, 91, 120, 225) and may facilitate interactions with APP, which also interacts with HSPGs in cholesterol rich microdomains (lipid rafts 64, 193). Such interactions seem to be favored in AAND pathogenesis, since APP, tau and asyn colocalize with HSPGs in AAND neuropathological lesions (51, 59, 109 197). HSPGs may facilitate interactions between asyn and tau (both localized to elements on the inside of the membrane) and PrP^{C}, which is typically found on the exterior surface attached via a GPI anchor (163, 232) and may themselves mediate transcellular protein movement, as has been suggested by studies of morphogen movement during *Drosophila* development (166), possibly by trapping interacting proteins in the extracellular space (232). Raft-associated interactions appear to be important in disease-associated misprocessing of tau, asyn and PrP mediated via fyn (131, 138, 188, 221), in aggregation (195, 230) and in disruption of signal transduction pathways in CNS dendrites (108, 117). Lipid association also drives oligomer and filament formation of Abeta, tau and PrP (44, 208, 221). In a very recent study by Binder and colleagues (170), a mAb specific for tau oligomer identified the presence of arachidonic acid as one of the requirements for early oligomer formation in cell culture. Similarly, the presence of membrane anchors and raft localization motifs plays an essential role in the development of characteristic lesion morphology of PrP-mediated disease (40); the removal of the GPI anchor has been shown to produce novel syndromes in transgenic models (43), while the removal of all of the multiple raft localization motifs on PrP blocks lesion formation and propagation entirely (16, reviewed in 209).

The relationship between asyn misprocessing and membrane localization in AANDs may be more complex than that of PrP and tau, since some, but not all disease-inducing mutations block raft-asyn association (75). Like PrP and tau, asyn is localized to lipid raft microdomains in presynaptic terminals, where it accumulates in dystrophic neurites associated with Parkinson's Disease and Lewy body dementia (81). Similarly, asyn fibrillization is favored by interactions with unsaturated fatty acids (173) but unlike tau, this is inhibited by saturated fatty acids (233). A particularly intriguing recent finding by Fang et. al. demonstrated a direct link between oligomerization and unconventional secretion in a study showing that higher-order oligomerization can drive exosome-mediated secretion of a wide variety of oligomerized proteins (70). This is particularly interesting given that tau, asyn and PrP are all substrates for fyn and related raft-associated srk tyrosine kinases (136, 138, 188), and that such interactions are associated with AAND pathogenesis (19, 110) and have potentially

self-regenerative features (i.e. by activating both the tyrosine kinase and its substrate 179). Such activation can result in fyn-mediated endocytosis via the caveolar pathway (204) or direct release of microvesicles to the extracellular space mediated via the SH4 domain of fyn (or other srk kinases) (34, 210). Regulation of endocytosis and exocytosis in neuronal growth cones by srk family kinases regulates endothelial apical endocytosis (77) and has been described in the marine snail Aplysia (223) suggesting that this is an evolutionarily conserved role for fyn-like Srk family kinases in diverse tissues. Developmental programs requiring high levels of localized membrane addition (e.g. neurite outgrowth) are dependent on the local presence of both srk family kinases and aggregation-prone proteins such as tau (20, 21) asyn (17) or Abeta (172) and are often abnormally reactivated in AANDs (26, 108, 174).

3. Cytopathological features linking aggregation and secretion in ANDDs

We have discussed the generation of abnormal tau, asyn and PrP oligomers as the most likely proximate cause of neurodegeneration in AANDs and proposed a common set of membrane-associated ligands for these proteins (e.g. HSPGs, signal transduction pathway kinases, fatty acids) which might mediate common aspects of their misprocessing, including their oligomerization, cellular colocalization and diversion into unconventional secretion pathways. Several features peculiar to neuronal AAND pathobiology that seem particularly likely to be important are discussed below.

Misprocessing of APP to Abeta 1-42 in early endosomes

So far, this discussion has focused the discussion on tau, asyn and PrP as aggregation-prone proteins immediately responsible for downstream neurotoxicity, and has ignored the contribution of aberrant APP misprocessing to Abeta in AAND pathogenesis, despite its well established importance in the pathogenesis of AD in particular (32, 94). However, it has now generally regarded as established that APP misprocessing to Abeta is the initiating event in the pathological cascade leading to AD, even if much of the proximate cytotoxicity driving neurodegeneration is mediated by tau (87, 125, 177, 180). The high cholesterol environment of rafts appears to be necessary for AAND associated misprocessing both in cell culture and in *in situ* AD models (64, 120, 198, 208). Furthermore, Abeta production and toxicity appears to play an important role in AANDs involving asyn and PrP as well as tau (48, 58, 134, 164, 198**)**. Most important for the present analysis is the major site of Abeta production from APP – the early endosome. Endosomal production of Abeta 1-42 RNAi experiments have shown that APP endocytosis requires the raft marker flotillin2 in neurons, and furthermore, that misprocessing of wild type APP to Abeta 1-42 is blocked by inhibition of endocytosis (191), as is the secretion of Abeta to the extracellular space (46). APP is recruited to rafts by the raft-associated tyrosine kinase fyn **(**155**)**, where its interactions with tau, asyn and PrP may play a role in both oligomerization and raft patching **(**163**)** leading to secretion of these proteins via either endocytosis and eventually exosome-mediated release **(**68, 70, 73, 176, 185**)**, or microvesicle shedding **(**145, 163). This similarity should result in extensive opportunities for co-oligomerization between tau, asyn and possibly PrP in endosomal processing, resulting in diversion of oligomerized proteins to the exosome pathway – schematized in Figure 3.

AAND-associated proteins interact with APP in lipid rafts and may affect A beta production. There is some reason to believe that tau may influence APP misprocessing to

Abeta in association with endosomes, since tau binds to and may modulate the activity of presenilin 1, an intrinsic membrane protein which serves as the gamma secretase responsible for completing the cleavage of APP to Abeta (207), and is the site of most mutations responsible for autosomal dominant familial AD. Similarly, PrP^{C} is normally endocytosed via a raft specific, flotillin2/clathrin dependent pathway (204), and it has been suggested that the conversion of PrP^{C} to PrP^{Sc}, like APP cleavage to Abeta, occurs during endosome formation. There is indeed some evidence that PrP conversion to misfolded PrP^{Sc} forms can increase the misprocessing of APP by increasing the activity of the so-called beta secretase, which cleaves APP to a extracellularly released fragment and a "C99" transmembrane domain (14). Asyn interactions with APP have also been shown to greatly increase the level of Abeta secretion from PC12 cells (121). Conversely, the observation that Abeta activates the srk family kinase Abl resulting in tau phosphorylation at sites crucial to disease-associated tau aggregation (34), is also consistent with the possibility that Abeta-induced tau misprocessing may occur in the context of endosome formation.

AAND-associated protein misprocessing may favor exosomal secretion by damaging autophagy-mediated protein turnover mechanisms. It has long been suspected that alterations in protein turnover mechanisms play a significant role in the cytopathogenesis of AANDs. Under normal conditions, much of the proteolytic turnover of small cytosolic proteins such as tau, asyn and very likely PrP as well is accomplished via the ubiquitin/proteosome pathway (88, 181, 218). The aggregation of these proteins blocks this pathway, apparently due to the steric limitations of the proteosome, resulting in the ubiquitination of tau and Asyn aggregates typically seen in AANDs (158, 220). This provokes the upregulation of the macroautophagy (or simply autophagy) pathway, producing endosomal and lysosomal hypertrophy (35, 36, 165, 167) presumably due to the diversion of proteosome-mediated turnover of AAND associated proteins to the autophagy pathway. It is now becoming clear that aberrant autophagy pathway function is a general phenomenon in AANDs, and increasingly appears that autophagy pathway insufficiency rather than overactivity is the key cytopathological factor (105, 220), reviewed in (153). Since autophagy can function to remove cytosolic debris from cells via lysosomes as well as recycle cytosolic components, this may provide a secretion route for aggregated or misprocessed proteins in AANDs, especially if lysosome-mediated proteolysis is compromised (see Figure 2). Specific inhibition of autophagy combined with tau overexpression results in tau aggregate formation even in cultured neuronal cells, with tau aggregates (104) and toxic cleavage fragments (129) accumulating in lysosomal compartments. Blockade of normal retrograde axonal transport of lysosomes in AD (23) or by specific mutation (178) appears to inhibit autolysosome function indirectly by preventing amphisome-lysosome fusion in the soma, which may favor secretion by diverting incompletely degraded cytoskeletal material into exosomal secretion pathways (Figure 2). Such secretion has been described as "exophagy" in yeast (2). It is quite possible that this kind of diversion into exosomal secretion pathways may apply generally in AANDs, as autophagy disruption also occurs to a significant extent in association with asyn, Abeta, and PrP^{Sc}-positive lesions in AANDs (154, 164). Moreover, the tendency of AAND associated proteins to disrupt retrograde transport of autophagosomes (229) could very well promote exosomal secretion of these proteins from ectopic locations in the distal axons, providing a mechanism for the long distance lesion propagation seen in AD (203) and other AANDs (9-11) - see further discussion below).

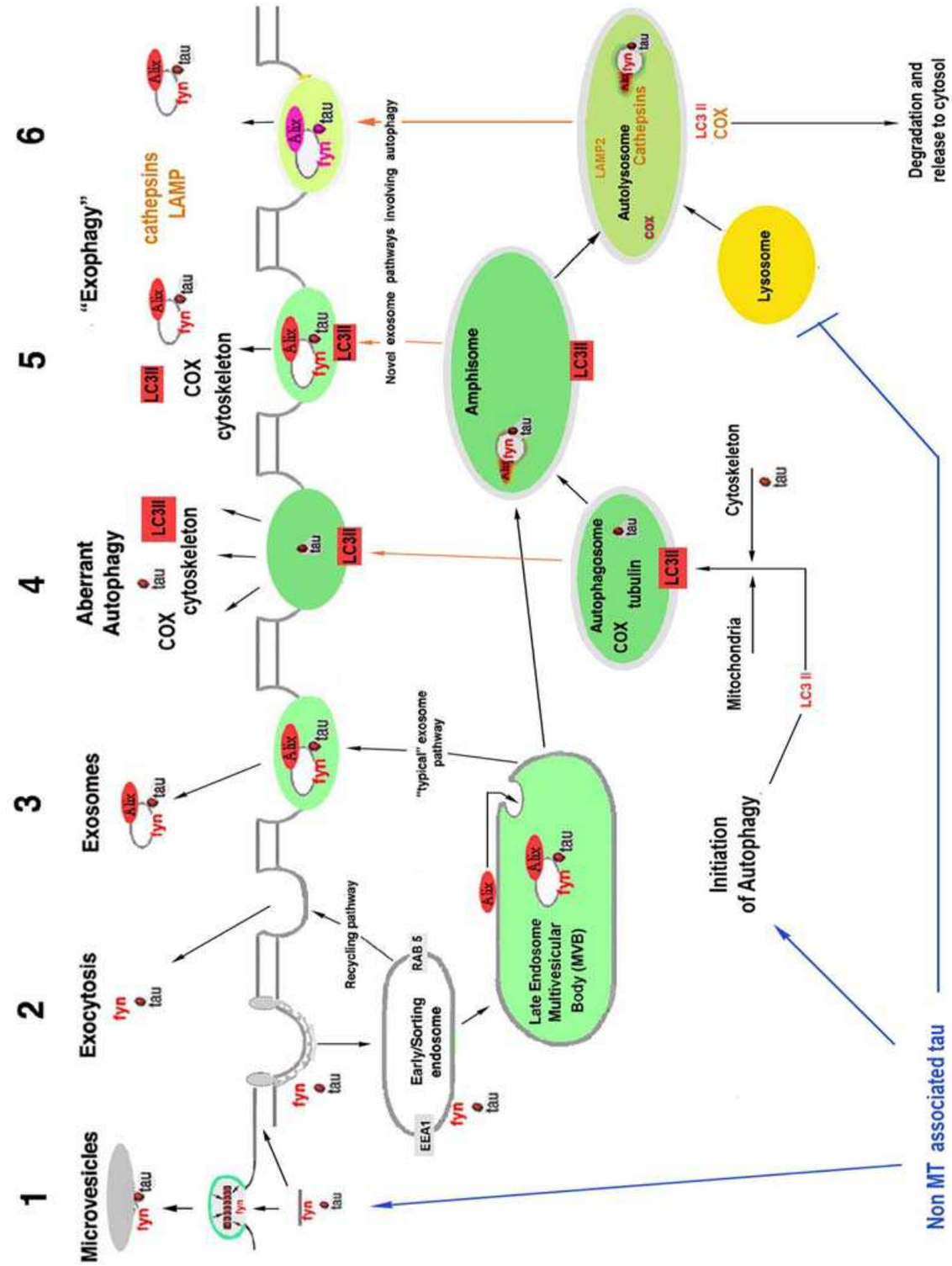

Fig. 2. Overview of possible secretion routes for AAND-associated proteins based on current literature Unconventional secretion has now been demonstrated for tau, asyn, PrP and Abeta in various model systems

This schematic illustrates how an aggregation-prone cytosolic protein with alternative membrane-associated ligands (in this case tau and fyn, respectively) might become aberrantly included in one of several possible vesicle trafficking pathways leading to unconventional release if it is released from its normal cytosolic ligand (microtubules) due to disease-associated conditions, which include hyperphosphorylation and microtubule loss, and which can be mimicked by overexpression (142). While tau is shown in this figure, the exosomal secretion pathways for Asyn, A beta, and PrP appear to be similar, especially since misprocessing of each of these proteins favors membrane-associated misprocessing (1) in association with the activation of autophagy (2) combined with disruption of downstream autophagic mechanisms that are necessary for the complete degradation of proteins in the autophagosome (3). While the secretion mechanism that has been identified for any of these proteins is nominally the "classic" exosomal pathway, marked by the presence of exosome–enriched proteins (e.g. Alix), it is likely that exosome secretion occurs via a number of closely related pathways that are associated to a greater or lesser degree with macroautophagy and lysosome-mediated protein turnover. Some of these pathways are indistinguishable from (or even included in) the "classical" exosome pathway (which does not involve lysosomal processing) and can be identified only via the identification of autophagosomal marker proteins (e.g cleaved LC3 (LC3II), cytoskeletal/mitochondrial proteins (COX, tubulins) and/or lysosomal markers (LAMP2, cathepsins) copurifed with exosomal/MVB markers and the AAND-associated protein in question. Involvement of autophagy-associated mechanisms to form a hybrid "exophagy" pathway (2) is particularly likely if misprocessing is associated with aggregate-induced impairment of autophagy, as occurs in AANDs. Secretion pathways are elaborated from Abrahamsen et. al. (2) and Nickel (163). (1) microvesicle shedding– this pathway is driven by srk kinase activity and oligomer-mediated "patching", but does not involve endocytosis, (2) endosome recycling pathway, (3) classic exosome pathway, (4) non-exosomal autophagosome dumping (commonly seen with tau overexpression models), (5-6) "exophagy" pathways either without autophagolysosomal formation.

Unconventional secretion may be linked to axonal transport and neuronal polarity defects caused by AAND-associated protein misprocessing. Another attractive area to look for common links between AAND associated aggregation and secretion of tau, PrP, asyn and APP is that of axonal transport and axonal identity. Each of these proteins is normally axonally localized (22, 127, 150), and the misprocessing of each protein has been shown to disrupt axoplasmic transport in AANDs and AAND models, (157, 162, 199, 200, reviewed in 183), while disruption of dynein/dynactin mediated transport produces a phenocopy of AAND-like syndromes (132). General abnormalities in axonal transport are likely relevant to common neuropathological characteristics of AANDs, such as the anterograde and retrograde propagation of lesions between distant areas of the brain and the disproportionate involvement of large neurons, presumably due to their inherently increased vulnerability to mitochondrial misdistribution and growth factor deprivation (160, 190, 206).

The reported nature of the disruptions of axonal transport has most often involved the obstruction of axonal transport and accompanied by neurodegeneration via what may be effectively an axotomy syndrome related to synapse loss and growth factor deprivation (157, 195) However, the more interesting possibility, at least with respect to lesion propagation, is that misprocessed tau, asyn or PrP could be itself aberrantly transported along the axon in ways that could account for disease-specific features of AANDs. There is a great deal of circumstantial and correlative evidence in favor of a major role for axonal

transport of vesicle-associated pathogens within the CNS, which closely resembles the movement of infectious prions within the brain (3, 53, 215). Interneuronal movement of HIV has recently been shown to involve PrP^{C} mediation (181) and the binding of a raft-localizing domain that also mediates Abeta and PrP^{Sc} localization to rafts (149), lending direct support to the operation of this mechanism in AANDs. The transfer of PrP^{Sc} from the gut to the CNS in diseases such as kuru and vCJD involves passage through lymphatic tissues where intercellular movement of both proteins and viral particles occurs via exosomes (215) the unconventional secretion pathway common to asyn, Abeta, PrP and tau (68, 73, 176, 185). Each of these proteins is associated with axonally transported vesicles (71, 76, 123, 127, 140, 141, 150, 230), sometimes in colocalization with (71) or functionally linked with one another (134) in synapses. Moreover, exosome release of PrP has recently been tied to synaptic function with specific neurotransmitters (135), illustrating one mechanism by which specific anterograde and or retrograde pathways might be targeted. The possible operation of common a "prion like" propagation of vesicle-associated misprocessed protein in AAND pathogenesis is further strengthened by the demonstrations that Abeta toxicity can be propagated from the peritoneal cavity to the CNS in a manner similar to ingested prions (65), and that vesicle-associated tau can be dendritically transported and secreted in an *in situ* tauopathy model (123, 141). Finally, numerous studies of LBD, AD and CJD pathology in human patients and/or disease models have now documented the selective colocalization of axonally transported tau and asyn in dystrophic neurites associated with neurofibrillary lesions (neuritic plaques) produced by APP and/or PrP based amyloids (81, 82, 109) suggesting that synergistic interactions associated with vesicle formation (presumably during endocytosis or endosomal processing) may play a role in the lesion overlap and risk synergy so often seen in AAND neuropathology and epidemiology.

Is polarity loss connected to the misprocessing and secretion of tau and other AAND-associated proteins?

Another aspect of axonal function that is of particular relevance to tauopathies and AD, but may well be involved in any or all of the AANDs under discussion, is the selective effect of tau misprocessing on axonal identity, process outgrowth and synaptic connectivity in AD and non-AD tauopathies. Tau is normally axonally localized in neurons (22) and plays a well-established role in axonal outgrowth (20, 34, 60, 235, reviewed in 91) and in the generation of axonal identity in at least some CNS neuron types (21, 34). Much of this developmental activity of tau involves interactions with the plasma membrane and signal transduction elements rather than MTs (20, 115, 235), and appears to be partly recapitulated in AD and tauopathy pathogenesis with the outgrowth of axonlike processes (neuropil threads). Another aspect of AD pathogenesis that reflects developmental tau function is the loss of neuronal polarity seen in the neuropathology of AD and non-AD tauopathies, which is manifested in a) the progressive movement of tau from the axons to the somatodendritic compartment with the development of neurofibrillary pathology (15, 89) and b) the origination of many tau-positive neuropil threads from the dendrites of neurons in AD (107, 174).

The link between AAND neuropathology and polarity loss accounts for important neuropathological and etiological peculiarities of AD, including: a) the mislocalization and trapping of signal transduction elements essential to the establishment of axonal identity and neuronal polarity, such as CRMP-2 (159, 228) and PAR1/MARK kinase (21), and b) the greatly increased risk (up to 19 fold) that traumatic brain injury (TBI) and chronic injury

caused by multiple concussions (CTE) poses for the development of neurodegenerative disease, AD in particular (152). Torsion and stretching injury to the brain resulting in occult axotomy of long tracts in the CNS is a major pathological feature in CTE (212), and can occur very close to the soma of the axotomized neuron without killing it (194). Such injury results in the accumulation of axonally transported asyn, APP, PrP and in some cases tau at the proximal axon stump of injured neurons that are reminiscent of axonal swellings containing these proteins in AANDs (15, 162, 212).

Studies in lower vertebrate (98, 99, 101) and mammalian (45, 144, 182) systems have consistently suggested that polarity loss induced by proximal axotomy could be a mechanism capable of linking axonal injury and the development of AAND-like neuropathology. Proximal axotomy induces ectopic axonlike sprouting (98, 182), the aberrant phosphorylation and missorting of cytoskeletal proteins (99, 100) and thus reproduces key aspects of AD neuritic pathology (26, 107, 174). Missorting of axonal elements such as tau can produce AD-like loss of function degenerative changes in the axon such as synapse loss (54) as well as somatodendritic hyperphosphorylated tau accumulation, which it does even at low levels of overexpression in murine transgenics (30, 86). Interestingly, tau induced neuropathology in tauopathy models produces a number of toxic changes in the dendrites that might shed light on the link between tau misprocessing and interneuronal tau transfer. Tau expression in models causes progressive dendritic degeneration (101) and has specific effects on dendritic MT number (103) and function (61) that resemble both AD pathology (27, 151) and the effects of proximal axotomy (72, 182 , 200, 101). A recent result of particular interest in this context is the recent demonstration by Ittner and co-workers (117) that ectopically localized dendritic tau mediates Abeta toxicity in a transgenic mouse tauopathy model. This finding highlights the possibility that Abeta-mediated tau misprocessing might be initiated by the aberrant juxtaposition of (normally axonal) tau with membrane-associated signal transduction partners that are present in dendrites, causing abnormalities in tau processing that lead to aggregation and eventually secretion, possibly via interactions with synaptic Abeta (71, 135). The dependence of neuronal polarization and axonal outgrowth on normal interactions between tau and localized membrane-associated tyrosine kinases (20, 21, 55) and the sensitivity of dendritic integrity to disruption of dendritic signal transduction pathways by mislocalized PrP (115) suggests that the relocalization of key proteins in AANDs might be a generally applicable mechanism in the misprocessing of AAND proteins by which normal cellular functions and interactions are replaced by abnormal ones by missorting events associated with damage to axonal transport and identity mechanisms.

4. Summary and conclusions

The aggregation of the AAND-associated proteins tau, asyn, PrP and APP/Abeta appears to be triggered by one or more post-translational events (cleavage/phosphorylation/ glycosylation) that redistribute charges so as to change the predominant secondary structure from an unfolded/alpha helical pattern to a beta pleated sheet pattern. This change is associated with and driven by familial disease mutations, and may also be favored by the interaction with hydrophobic elements in cellular membranes and/or the binding of perimembranous polyanions (e.g. HSPGs), raising the interesting (and heretofore largely ignored) possibility that aggregate formation in AANDs may depend at least in part on interactions with cellular membranes. The relationship between membrane associated misprocessing and the cytopathogenesis of AANDs is summarized in Figure 3.

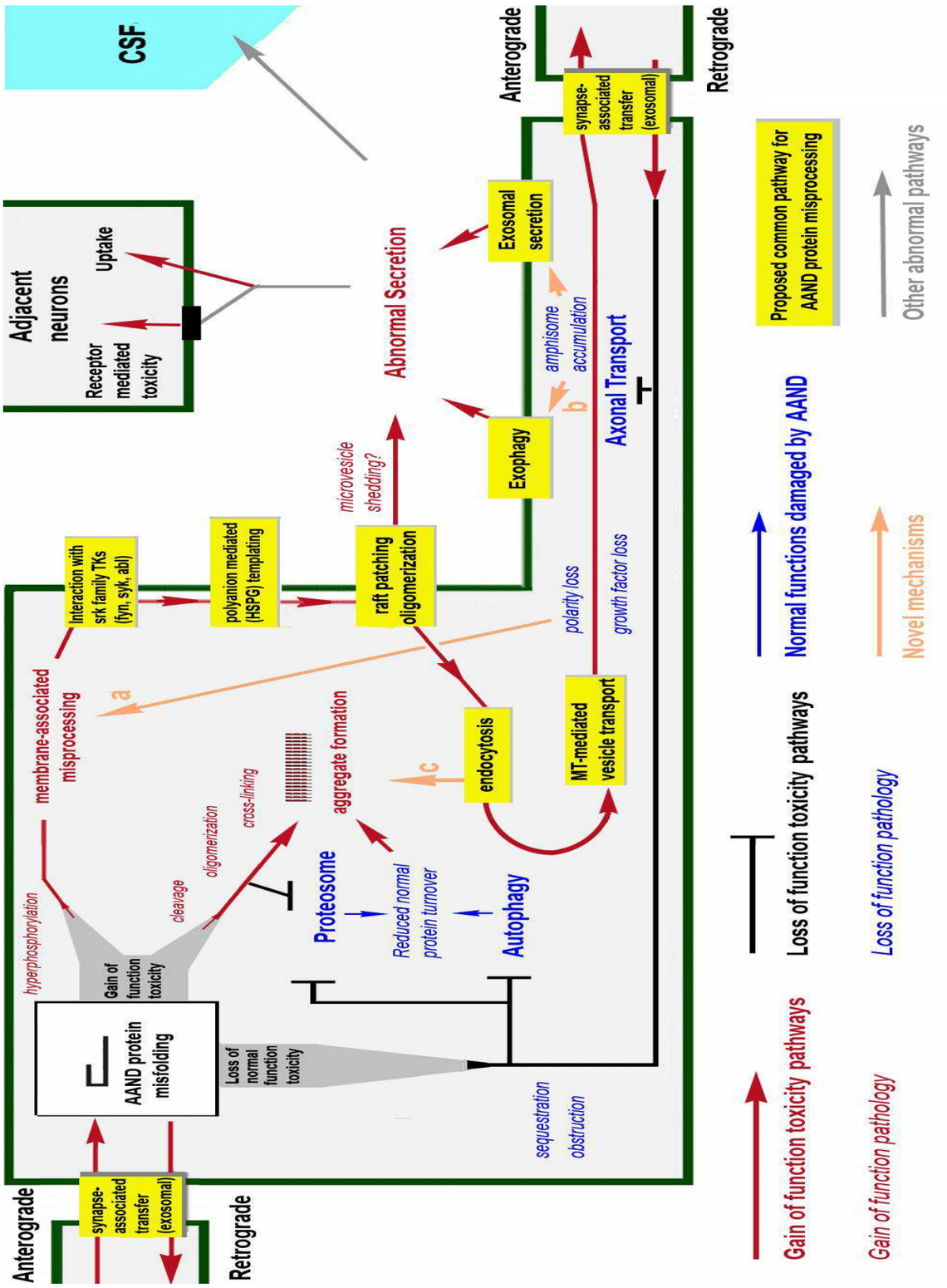

Fig. 3. Summary of common cellular misprocessing pathways linking aggregation and interneuronal transfer of AAND-associated proteins

Hypothetical scheme by which the initial misfolding of AAND-associated proteins (tau asyn, PrP and Abeta) produces intracellular aggregates and other typical AAND cytopathological features in combination with the propagation of this pathology to adjacent, presynaptic and postsynaptic neurons. AAND cytopoathology is produced via a combination of pathological gain of function and loss of function toxicity pathways as indicated. Recent evidence for a common membrane associated misprocessing route that causes the diversion of endocytosed proteins into abnormal vesicle trafficking pathways is highlighted, as it links oligomeri formation with interneuronal transfer and offers multiple opportunities for the colocalization and synergistic interaction (e.g. co-oligomerization) between AANDs at the cellular level necessary to explain the clinical and neuropathological evidence for synergy between AANDs. The classical cytosolic route for aggregate formation is also shown. Novel relationships suggested by recent studies (peach - see text for discussion) that account for key common and/or specific AAND features and could be fruitful foci of future research include links between a) axonal damage, protein mislocation due to polarity loss, and aberrant toxic interactions with dendritic signalling pathways and b) membrane-associated oligomerization and aggregate formation are shown as well, as c) the possible link between damage to axonal transport (failure of normal autophagosome/lysosome colocalization) and unconventional secretion.

Current evidence indicates that initial protein misprocessing in AANDs becomes irreversible due to cleavage and/or crosslinking events that are favored by and occur during the oligomerization/aggregation process and that novel emergent pathological interactions due to polymerization eventually become dominant in the affected neuron, leading both to the dysfunction and death of the aggregate-containing neuron and the spreading of the aggregation tendency to other neurons, where the degenerative cycle is repeated. The retrograde and/or anterograde transfer of membrane associated, oligomerized, toxic protein to other neurons involves axonal propagation of endosome-derived vesicles via transport mechanisms that may have been altered by aggregate-mediated toxicity. Lesion spreading occurs either 1) via a toxic consequence of aberrant neuronal function, such as the loss of transneuronal trophic factor transmission or the increased generation of toxic byproducts of degeneration, or 2) via the actual transfer of misprocessed proteins from one neuron to another. Evidence supporting the latter possibility (that lesion spread occurs via actual protein transfer in AANDs) has accumulated recently, as specific secretion, uptake, transfer and interneuronal toxicity transfer has now been observed for each of these proteins (47, 57, 73, 74, 75, 85, 123, 124, 128, 135, 140 - summarized in Table 1) and a common unconventional secretion pathway (i.e. exosome-mediated secretion) has been identified for PrP and Abeta (73, 176) and (quite recently) asyn and tau (68, 185). A hypothetical common misprocessing pathway for these proteins in AANDs is schematized in Figure 3.

The focus of this discussion has been on the shared characteristics of tau, asyn, PrP and Abeta that could allow each to a) associate with signal transduction elements in membrane raft domains and b) interact and oligomerize in association with elements capable of driving endocytosis (HSPGs, each other, possibly RNA, possibly via acidification driven charge-charge interactions) under circumstances which allow entry to exosomal secretion pathways, possibly via modifications induced in protein turnover mechanisms (autophagy) by aggregate toxicity. In particular, I have focused on whether this hypothesis is consistent with the now voluminous evidence that AANDs involving tau, asyn, PrP and APP misprocessing overlap one another in their etiology and pathogenesis, and whether and how well this hypothesized common link between aggregation and lesion propagation accounts for the

peculiarities of a specific protein–disease pair (tau and AD). While the necessarily general nature of this analysis precludes the accurate identification of emergent common mechanisms of AAND pathogenesis in any detail, it is hoped that it can provide a framework that may help guide further investigation in this rapidly changing field.

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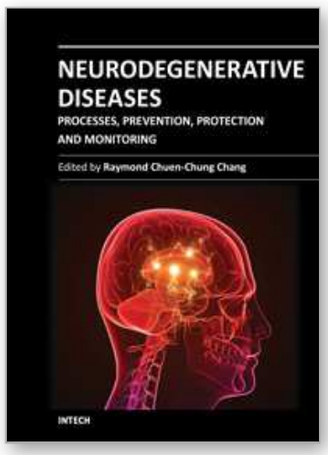

Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring

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Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring focuses on biological mechanisms, prevention, neuroprotection and even monitoring of disease progression. This book emphasizes the general biological processes of neurodegeneration in different neurodegenerative diseases. Although the primary etiology for different neurodegenerative diseases is different, there is a high level of similarity in the disease processes. The first three sections introduce how toxic proteins, intracellular calcium and oxidative stress affect different biological signaling pathways or molecular machineries to inform neurons to undergo degeneration. A section discusses how neighboring glial cells modulate or promote neurodegeneration. In the next section an evaluation is given of how hormonal and metabolic control modulate disease progression, which is followed by a section exploring some preventive methods using natural products and new pharmacological targets. We also explore how medical devices facilitate patient monitoring. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

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