biologics

MDPI

Review

Vesicular Transport and Amyloids: The Growing Relationship

Arun Upadhyay

Department of Bioscience and Biomedical Engineering, Indian Institute of Technology Bhilai, Bhilai 491002, Chhattisgarh, India; arun@iitbhilai.ac.in

Abstract: Protein aggregation may lead to detrimental changes in brain and several other tissues. Amyloids or large protein aggregates are formed in different brain areas under multiple diseases classified as proteinopathies. However, our understanding of the initiation, elongation, and spread of amyloid aggregates is limited. Our current knowledge about these diseases is generic and we lack specific mechanisms for several diseases affecting memory, movement, and behavior. Multiple studies have indicated the involvement of vesicular transport in the spread of aggregates formed inside the brain. For example, the trafficking of amyloid precursor protein (APP) occurs from Golgi to Endosome using an adapter protein complex. Amyloids, once formed, may also affect cholesterol (an important membrane constituent), homeostasis, and overall membranous transport. A disruption of vesicular transport could be deleterious for synaptic neurotransmission. Alterations caused by amyloid proteins in vesicular transport may form a feedback loop and thus contribute further to the pathogenesis of Alzheimer's disease (AD) and many others. In this review, we are providing recent updates on this crisscross puzzle and exploring an evolving correlation between amyloid formation and vesicular transport.

Keywords: amyloids; neurodegeneration; vesicular transport; synapse; extracellular vesicles

Citation: Upadhyay, A. Vesicular Transport and Amyloids: The Growing Relationship. *Biologics* **2024**, *4*, 376–389. https://doi.org/10.3390/biologics4040023

Academic Editor: Yasunari Matsuzaka

Received: 27 August 2024
Revised: 27 September 2024
Accepted: 8 October 2024
Published: 11 October 2024

1. Introduction

Amyloid beta (Aβ) peptides are the primary component of the plaques deposited extracellularly in AD patients' brain tissues. These small peptides are produced from cleavage of amyloid precursor protein (APP) and exhibit multiple effects on vesicular transport in neuronal cells [1,2]. APP and its cleavage products, including Aβ can influence vesicular transport through its packaging into vesicles or its secretion into the extracellular space, followed by the intracellular transport of these amyloid-containing vesicles in both anterograde and retrograde directions [3–5]. It has been observed that Aβ can directly interfere with the cellular transport and normal trafficking of vesicles within the neuron, potentially disrupting the delivery of essential cargoes to their intended destinations [6,7]. Additionally, Aβ can open up membrane pores and allows the leakage/influx of Ca^{2+} leading to the loss of mitochondrial homeostasis and the death of neurons [8]. Moreover, Aβ peptides and their aggregatory forms, for example, oligomers, fibrils, and plaques, can alter multiple other pathways leading to a perturbed homeostasis in the neurons [6,9]. For example, Aβ affects cellular cholesterol homeostasis that may contribute to the neuropathological changes associated with perturbed vesicular trafficking in AD [10]. Aβ has also been demonstrated to induce rapid changes in the transport of brain-derived neurotrophic factor (BDNF)-containing vesicles, with BDNF and the amyloid precursor protein (APP) co-localizing with low-density lipid vesicles [11,12].

Vesicular transport may also play a prominent role in the spread of APP, its cleavage products, including Aβ monomers and oligomers [13,14]. Multiple mechanisms have been identified that indicate the direct involvement of membrane-bound vesicles or sac in the packaging, transport, and targeted delivery of Aβ-containing cargoes [15,16]. Several animal-based studies have reported that Aβ-enriched extracts can travel through body fluids from the site of their injection to affect distantly located regions/tissues [17,18]. An

abundance of evidence supports a prion-like transmission of Aβ peptides [19,20]. However, our current understanding is yet to be substantiated. Overall, the linkage between the neuronal vesicular transport system and amyloids, particularly Aβ, is a crucial component in the AD pathomechanism and other neurodegenerative disorders. Therefore, interfering with the crosstalk between amyloids and vesicular transport may have widespread consequences. These include impaired synaptic signaling and neuronal survival [21]. A detailed understanding of the pathways and mechanisms that lead to amyloid-mediated interference in vesicular transport and the exploration of possible approaches to alleviating pathogenic changes may help devise new therapeutic avenues for the development of effective treatments and the prevention of neurodegeneration [5].

2. Protein Aggregates, Amyloids and Cellular Homeostasis

Proteins are crucial players in cellular homeostasis. A balanced environment inside and outside of a cell requires a healthy pool of proteins that can continuously perform their physiological roles. To achieve that, proteins remain in a unique three-dimensional structure all the time [22]. However, external stresses and internal perturbances may affect the structural integrity of proteins and thus disrupt their physiological functions [23]. Some changes may interfere with the folding (by molecular chaperones) of newly synthesized proteins. Several mutations that can alter the structure, solubility, and stability of a protein and can lead to conformational changes and subsequent protein aggregation. Similarly, a few intra- or extracellular factors may lead to the misfolding of existing proteins [24,25]. Intracellular factors include mutations, posttranslational modifications, increased proteotoxicity, inefficient chaperoning, etc., while extracellular factors include pH, salt concentration, temperature changes, etc. Continuous misfolding of proteins may generate enormous proteotoxicity inside cells. The aggravated load of misfolded proteins may in turn lead to the aggregation of misfolded proteins and the generation of inclusion bodies [26]. This cycle continues and leads to a systemic failure of the cellular protein quality control (PQC) system, generating amyloids and intracellular inclusion bodies. Interestingly, amyloid formation may have several protective and beneficial effects across different species and organisms. For example, amyloidic structures from proteins involved in bacterial biofilms, protective eggshells in insects and fish, peptide hormone storage, and memory formation in mammals have previously been reported [27].

The formation of highly stable, ordered, repetitive cross-β sheet structures called amyloid fibrils, may lead to several neurodegenerative diseases, including Alzheimer's and Parkinson's disease [28]. Nonetheless, a detailed understanding of the mechanisms involved and the roles of additional co-factors in the etiology of these diseases is not fully developed. The oxidation of proteins due to intensive oxidative stress, particularly during aging, is a very common factor that promotes the aggregation of proteins [29]. As shown in Figure 1, factors like molecular crowding, mutations, stresses, and aging-related changes may increase the likelihood of protein misfolding and the formation of amyloids, which eventually contributes to a high proteotoxic load [30,31]. Additionally, studies have indicated that several post-translational modifications (PTMs), such as glycosylation, phosphorylation, and oxidation, can influence the aggregation behavior of proteins [32]. Overall, a highly complex interplay between protein aggregation, amyloid formation, and accessory co-factors is a key aspect of the pathogenesis of neurodegenerative diseases. A holistic approach toward the investigation of these molecular pathways associated with amyloid formation may develop a better understanding of disease pathologies and is crucial to the development of effective therapeutic strategies.

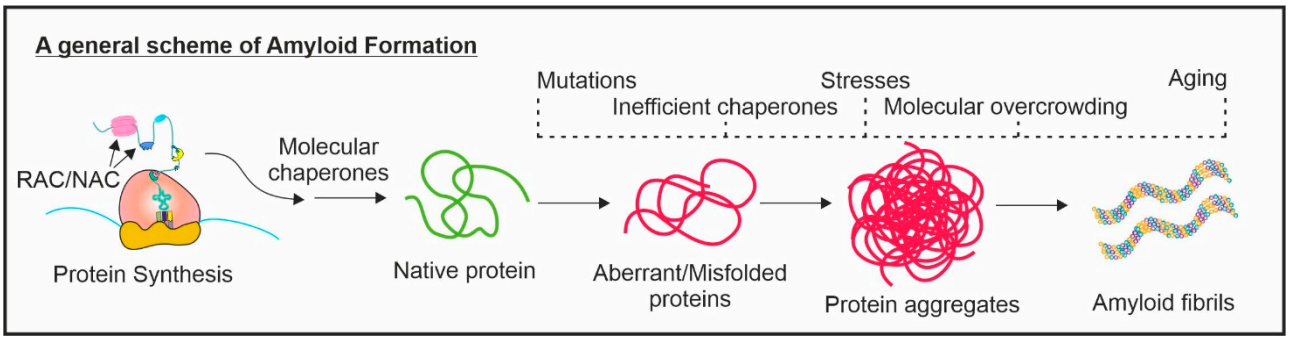

Figure 1. Schematic overview of amyloid formation. Cellular proteins, after being synthesized by ribosomes, are folded into their native conformation by molecular chaperones. However, due to several intracellular or extracellular factors, proteins may misfold and start aggregating. Sometimes, aggregation-prone proteins tend to attain a highly structured and thus stable conformations called amyloids.

3. Vesicular Transport

Vesicular transport is a process by which cellular components are transported via small membrane-bound sacs called vesicles (please see Figure 2). The vesicles facilitate the movement of substances/molecules across different compartments of a cell and from one cell to another [33,34]. Vesicular transport involves formation of a sac from a membrane through a process called budding. The vesicles contain highly specific cargoes and sends those to the target membranes precisely. Vesicles can recognize and fuse with the correct target membrane [35,36]. These vesicles may exist in multiple forms and take part in different pathways by utilizing distinct coatproteins and GTP-binding proteins to facilitate their formation and functioning. Examples of vesicles are clathrin-coated vesicles, COPI-coated vesicles, and COPII-coated vesicles [37,38]. Each type of vesicle is specialized in playing crucial roles in transport of proteins and lipids. Following which, the correct target delivery requires fusion with a designated target and release of cargo selectively. SNARE proteins play vital role in the fusion of vesicles [39,40]. They mediate the interaction and merger of vesicles to the fusion sites and hence facilitate the delivery of cargo to the appropriate location [41,42]. In summary, vesicular transport enables selective and precise regulation of the exchange of material between cell compartments. Their roles are investigated and established in the secretion and uptake of external material and the transportation of enzymes to the cell organelles. Several reports in the past have indicated that this mechanism of transportation may also play critical roles in the spread of amyloidic proteins and hence the toxicity caused by pathogenic amyloid aggregates [43,44]. Consequently, the formation of amyloids and their interaction with cellular membrane components, including vesicles, may affect and disrupt various processes including vesicular transport system [3]. In next few sections, a brief overview of this undefined relationship between amyloids and vesicles is discussed.

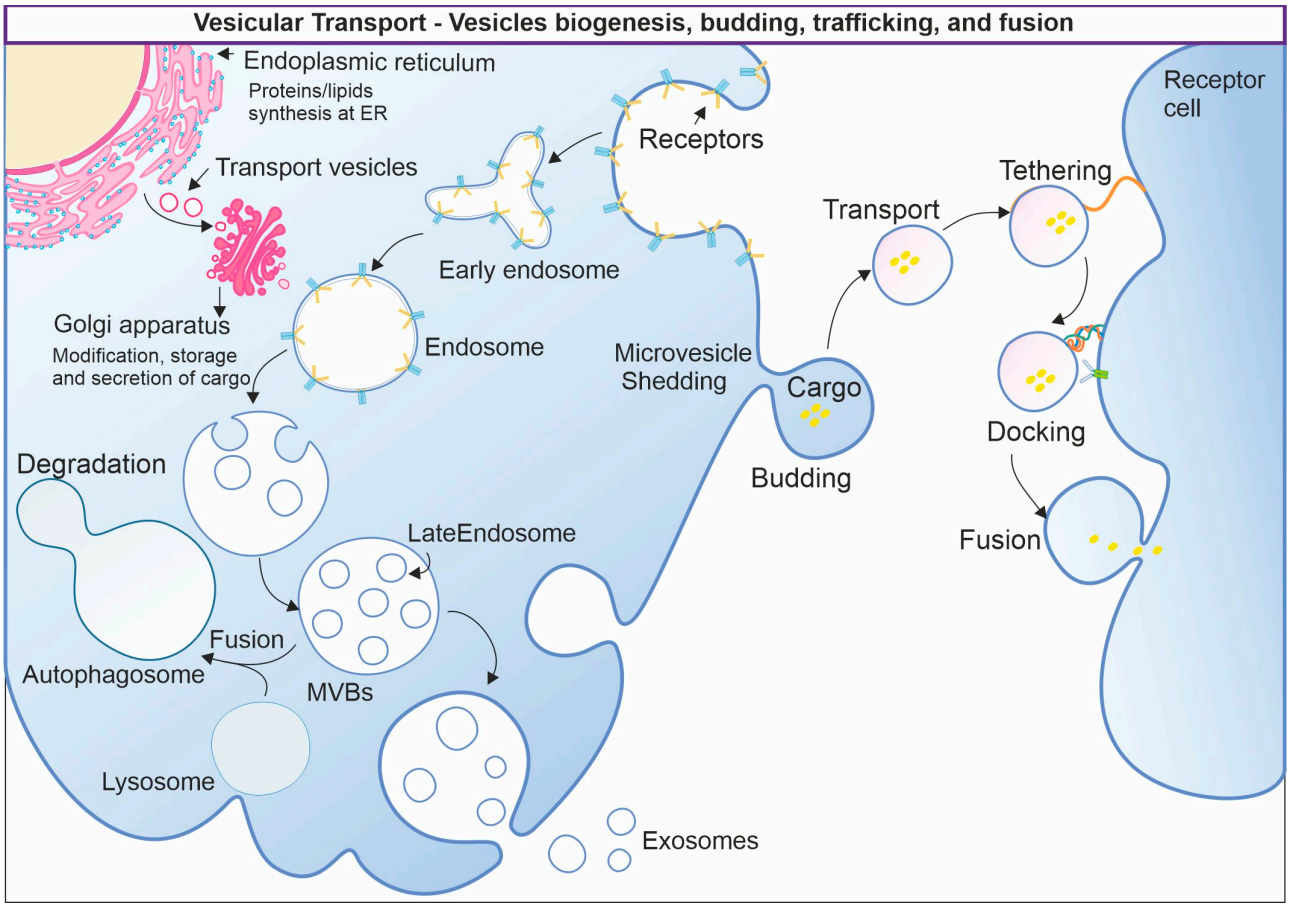

Figure 2. An outline of the crucial steps involved in a vesicular transport system. The secretory pathway involves the budding of transport vesicles from the ER, the transport of content away to the cis side of a Golgi, and the release of the cargo on the trans side. These vesicles may fuse with cell membranes or endosomes and may later fuse with lysosomes. Early endosomes are formed from membranes and extracellular components to target materials at late endosomes, which can later be delivered to lysosomes for degradation. Cargo selection, the deformation of the plasma membrane bilayer, and its breaking off into an extracellular transport vesicle (budding) followed by their correct targeting (tethering, docking, and fusion) are highly regulated events.

4. How Does Amyloid Interact and Interfere with Vesicular Transport?

Vesicular transport is a highly critical process in neurons that carries out the trafficking and distribution of various cargoes; for example, signaling molecules and neurotransmitters to the appropriate cellular locations [36,40]. This dynamic and highly regulated mechanism is critical for neuronal function, synaptic transmission, and overall homeostasis in the brain [21]. However, growing evidence suggests that amyloid formation in AD can have a profound impact on vesicular transport, leading to perturbed neuronal homeostasis and contributing to the pathogenesis of AD [45]. As shown in Figure 3, one major disruption induced by Aβ proteoforms is leaky membrane pores leading to perturbed Ca^{2+} homeostasis [8]. The interaction of Aβ peptides with membrane phospholipids and gangliosides may also contribute to porous or leaky membranes [46]. In addition, the presence of Aβ has been observed to alter cholesterol metabolism and vesicular traffic, contributing to the neurodegenerative changes seen in the AD brain [10]. Cholesterol, a crucial component of membranes in neurons, plays a vital role in the proper functioning of vesicular transport mechanisms [47]. In AD brains, Aβ accumulation leads to disruptions in cholesterol metabolism, and thus can lead to impairments in vesicle formation, trafficking, and fusion. This, in turn, impairs neuronal functions and contributes to AD

pathologies [48]. Similarly, Aβ oligomers also destabilizes membranes by lowering the levels of phosphatidylinositol-4,5-bisphosphate [49].

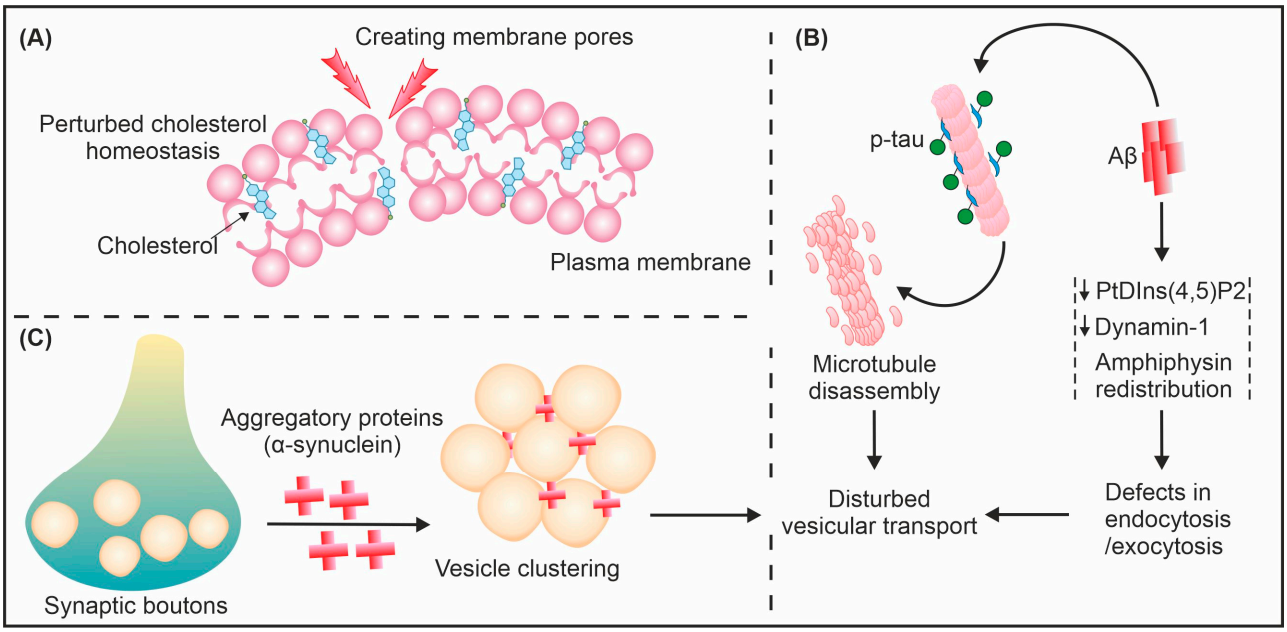

Figure 3. Protein aggregates and amyloid may alter membrane integrity and the vesicular transport system in multiple ways. (**A**) Pore formation by oligomeric or fibrillar aggregates is a common method, along with interfering with cholesterol metabolism to destabilize the lipid bilayer. (**B**) In AD brains, both amyloid beta and tau proteins may affect vesicular transport by altering different important players in the pathway. While hyperphosphorylated tau deposition leads to the destabilization of microtubules, the roles of Aβ in perturbing vesicles via multiple pathways are known. (**C**) Similarly, α-synuclein may lead to vesicle clustering, causing restricted vesicle trafficking and cargo transport.

The presence of Aβ and other associated amyloid species inside vesicles can lead to cascading effects on the dynamics of vesicular transport, possibly leading to the disturbances in various cellular processes contributing to neurodegeneration. The small Aβ peptides may affect the essential steps of endocytosis and exocytosis via multiple pathways. For example, Aβ leads to the inhibition of dynamin-1 that may end up in the accumulation of amphiphysin at the membrane, compared to the cytoplasm of cultured primary hippocampal neurons. This may lead to perturbed synaptic vesicle endocytosis [50]. BDNF is a critical neurotrophic factor that often supports the survival and function of neurons [51]. The precise trafficking of BDNF is essential for maintaining neuronal health. Interestingly, APP and Aβ have been observed to co-localize with low-density lipid vesicles, suggesting a potential disruption in the normal transport of these important signaling molecules. Another study in Tg2576 mice proposed that Aβ leads to a reduction in Uchl1, a deubiquitinase enzyme, and causes a ubiquitin-mediated disruption in the retrograde trafficking and signaling of TrkB/BDNF [52]. BDNF signaling deficits could be altered by γ-secretase inhibitors [53]. The impairment of BDNF trafficking by Aβ can have far-reaching consequences, including the disruption of synaptic plasticity, neuronal survival, and overall neuronal function [53,54].

The interplay between the Aβ- and adaptor protein complex AP1-1B-mediated transport of APP may also regulate vesicular transport [55]. Many proteins involved in APP processing, endocytic recycling, and intracellular transport can be affected by amyloid-related disruptions to these pathways, leading to detrimental consequences [56]. Overall, the disruptive effects of amyloids on multiple aspects of vesicular transport may play a key role in the pathomechanism of neurodegenerative diseases like AD. Interestingly, the impact of amyloids on vesicular transport is not limited to Aβ peptides alone. Multiple other

disease-associate amyloidogenic proteins, for example, α-synuclein (in Parkinson's disease), superoxide dismutase 1 (in amyotrophic lateral sclerosis), and huntingtin (in Huntington's disease), also indicate a possible alteration in vesicular transport mechanisms [57–59]. For example, α-synuclein may lead to the clustering of vesicles and hence restrict vesicle trafficking and the transport of neurotransmitters [60]. This emphasizes the impact that amyloid-mediated vesicular transport impairments may play in the pathogenesis of various neurodegenerative disorders.

5. Consequences of Amyloid-Induced Vesicular Transport Disruption

The disruption of vesicular transport by amyloid proteins, particularly Aβ, can have far-reaching consequences for neuronal function and overall brain health. One of the key consequences is the impairment of neurotransmitter release and synaptic transmission. As stated earlier, vesicular transport is essential for the trafficking and delivery of neurotransmitters to presynaptic terminals, where they can be released into the synaptic cleft and facilitate neuronal communication [61]. Disruptions in this process, as a result of Aβ accumulation, can lead to alterations in the availability and distribution of neurotransmitters, ultimately impairing synaptic function and contributing to the cognitive deficits observed in Alzheimer's disease [62]. Furthermore, the disruption of vesicular transport can also impact the trafficking and delivery of other essential cargoes, such as signaling molecules, cellular organelles, and neurotrophic factors, to their intended locations within the neuron [63,64]. This can have cascading effects on many cellular processes like neuronal survival, synaptic plasticity, and overall neuronal homeostasis. For instance, the impairment of BDNF trafficking by Aβ can compromise the trophic support and survival of neurons, leading to neurodegeneration and cognitive decline.

6. Vesicular Transport Facilitates Amyloid Propagation

The processing of APP by a series of proteases leads to the secretion of Aβ peptides in extracellular space. APP is cut by β- and γ-secretase consecutively to release Aβ fragments of varying lengths [65]. The monomeric Aβ peptides may form multiple types of assemblies leading to the formation of oligomers and fibrils which may further form large insoluble amyloid plaques. The co-existence of multiple distinct forms of Aβ peptides makes it difficult to characterize these species and draw conclusions about their toxicity [66]. In fact, a series of studies indicate that soluble oligomers are the drivers of pathogenicity, including synaptic loss at the initial stage of the disease [67–70]. On the other hand, another set of studies focus on the fibrils as the most toxic species of Aβ peptides and emphasize that it is amyloid plaques that lead to neuronal dystrophy and degeneration [66,71,72]. Despite Aβ alone does not cause entire destruction in AD brain, and a conclusive correlation between amyloid fibrils andneurodegeneration is yet to be established, the amyloid hypothesis is the most accepted theory explaining AD pathology [73,74]. However, we do not have a well-defined understanding of the pattern of distribution of amyloid pathology in the patient brain, either spatially or temporally. Most probably, plaques appear first in the neocortical regions of the AD brain and then spread to allocortex and other subcortical brain regions [75–77].

Multiple studies propose a prion like seeding and the spread of Aβ in AD mice and patient brains [19,20,78]. Oligomeric assemblies may seed and start the polymerization of Aβ monomers and other cellular proteins. As shown in Figure 4, the propagation of these assemblies following the injection of preformed assemblies, as reported in multiple independent studies, indicates that the neuronal transport system possibly plays a vital role in this propagation. Sinha et al. recently showed that patient-derived Aβ-containing exosomes may act as vehicles that propagate seeds in neuronal cell culture [79]. Cell-to-cell propagation could be a possible hypothesis, but conclusive evidence establishing an active neuron-to-neuron transport of Aβ assemblies is missing. A passive diffusion of Aβ assemblies is reported in a transplantation experiment, where wildtype neurons were grafted onto AD mice with Aβ pathology [80]. A few studies using intravenous injections

of Aβ-rich extracts have indicated the possibility of the vascular transport of Aβ, possibly via the involvement of immune cells [17,18,81]. Other studies elaborating the mechanism of Aβ peptide spread have indicated that these peptides are packaged into intraluminal vesicles and released in multivesicular bodies (MVBs). Following MVB fusion with a membrane, the vesicles (and the Aβ peptides) are released in the form of exosomes from the cell membrane into the interstitial spaces [82,83].

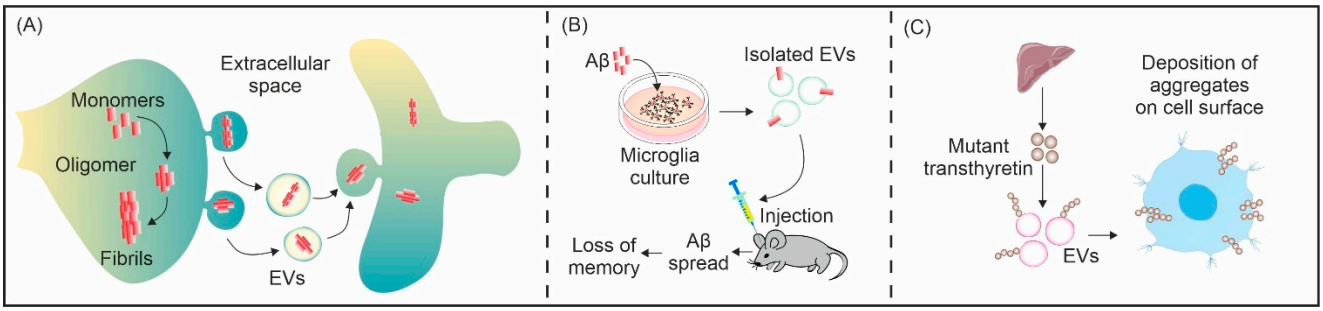

Figure 4. Vesicular transport may play vital roles in the transmission of protein aggregates and amyloids from one cell to another. (**A**) This could be achieved by a mechanism very similar to how prion proteins are transported from neurons to neurons or other glia cells utilizing vesicle budding and endocytosis. (**B**) A similar transport of Aβ peptides was observed in microglia cell culture where EV-packaged Aβ peptides were injected in transgenic AD mice and spread to other brain regions. (**C**) Apart from the brain, vesicles are important for the delivery of protein aggregates to other organs also. For example, mutant forms of transthyretin are carried by EVs and delivered to other cells' surfaces.

Vesicle transport plays vital roles in the propagation of amyloids in non-neuronal cells of the brain also. In a recent study, cultured microglia-derived exosomal vesicles treated with Aβ oligomers were introduced in a mouse brain using stereotaxic injection. The study indicated a spread of Aβ to brain regions distinct from the site of injection. This spread further led to signs of hippocampal memory loss [84]. Vesicular transport is essential for amyloid transport, including both release and propagation of amyloid assemblies from one cell to the other in many other organs [85]. Moreover, vesicle-mediated transmission and aggregation of amyloidogenic proteins secreted from organs other than brain have also been reported. For example, transthyretin, produced in the liver, binds to human serum-derived EVs and is deposited onto the surface of cultured cells [86]. Vesicles may impact the deposition and toxicity profile of amyloid proteins and hence the overall progression of neurodegenerative changes [87,88]. A well-regulated release of Aβ peptides and assemblies may facilitate their propagation and thus help amplify the spread of toxicity. Additionally, the packaging of Aβ and its C-terminal fragments into vesicles, followed by their release from the membrane into the extracellular environment, and the subsequent intracellular transport of these amyloid species, can contribute to the propagation of pathological processes within the brain [89,90]. Overall, the transport of amyloid-containing vesicles can facilitate the spread of these toxic species throughout the neuronal network, potentially leading to the recruitment of additional neurons into the pathological cascade and the exacerbation of neurodegeneration.

Amyloid-containing vesicles may influence the aggregation kinetics and behavior of Aβ peptides. They may affect the structural features of the growing fibrils by inhibiting the elongation of fibrils, and may favor the generation of shorter assemblies that potentially contribute to an increased toxicity [87,88]. Membrane trafficking is highly crucial for amyloid precursor protein (APP) processing and amyloid beta peptide secretion. Aβ peptides may possibly bind to the plasma membrane and affect the membrane's integrity and trafficking in multiple ways. In type 2 Diabetes mellitus-affected cynomolgus monkey brains, elevated cholesterol levels lead to disturbances in endocytic pathways and Aβ and APP accumulation. The perturbed membrane may also perturb lysosomal machinery

affecting the degradation of Aβ aggregates further [13,91]. Aging is another factor that contributes to alterations in APP trafficking and Aβ production. An upregulation in APP endocytosis with aging leads to increased production of Aβ [92]. Overall, dysregulated membrane trafficking and altered endosomal transport are potential markers of degenerated AD brains. These studies indicate a strong connection between membrane integrity and Aβ production.

7. Vesicular Transport System Plays Vital Role in Tau Propagation

Tau is the other pathological protein candidate causing widespread proteotoxicity in AD brains. Evidence suggests that the pathological forms of tau can propagate from affected brain areas to the nearby healthy areas of the brain, resembling a mechanism often used by prion proteins [93,94]. The prion-like propagation means an active and well-regulated process of transcellular diffusion of proteins via extracellular space. AD mouse and human brain extracts may induce tau pathology by propagating pathological proteins into the neurons [95–98]. The injection of synthetic tau fibrils in mouse overexpressing mutant human tau (P301S) leads to the formation of tangles in the brain regions away from the site of injection [99]. Extracellular tau aggregates may also be internalized and play a crucial part in the formation of fibrillar aggregates from intracellular tau, with an inherent tendency to diffuse from one cell to another [100,101]. Synaptic connections in neurons may also contribute to the propagation of tau tangles [102]. Several studies have previously reported the presence of phosphor-tau-containing extracellular vesicles in transgenic mouse brains and AD patients' blood and CSF samples [103–106].

There are multiple routes of tau propagation, including packaging into microvesicles, followed by release and uptake. The internalization of tau takes place by the cytoplasmic exosomes (also referred as intraluminal vesicles) present in multivesicular bodies and their release in extracellular space thereafter [106]. The internalization of tau in large vesicles (called ectosomes) has also been observed via the evagination of plasma membranes [107]. The pathogenic aggregates of tau may also develop pore-like formations in plasma membranes that may help further transmission of the protein [108–110]. Notably, a detailed understanding of how vesicular transport effectively propagates Aβ, tau, and other aggregation-prone proteins may offer promising avenues for the treatment of amyloidopathies. By enhancing vesicle recycling and modulating trafficking, we can alter the spread of and toxicity caused by amyloid proteins.

8. Amyloids, Vesicles, and Transport—Avenues for Future Therapeutics

Overall, amyloid beta (Aβ) can significantly impact various aspects of vesicular transport within neurons. On the other hand, vesicular transport plays vital roles in the packaging and propagation of amyloids within and outside of cells. For example, Aβ and C-terminal fragments can be packed into small vesicles and released extracellularly and later could be transported intracellularly in both directions. Additionally, impaired vesicular trafficking exacerbates synaptic dysfunction and contributes to the propagation of amyloid pathology. For instance, a disrupted vesicular transport mechanism leads to the accumulation of amyloid aggregates in brain tissue and aggravates the neurotoxic environment. Similarly, this interplay between amyloid and vesicle transport may negatively affect the synaptic function. Following the disruption of vesicles by amyloid proteins, a reduction in the release of neurotransmitters may lead to impaired neuronal communication. Notably, the disruption of vesicular transport by amyloids is not limited to Aβ and can also occur in other neurodegenerative disorders. This highlights the broader relevance of amyloid-mediated vesicular transport disruption in the field of neurodegeneration.

Investigation of the interactions between amyloids and vesicular transport machinery components may offer valuable insights into the causative mechanisms and provide new tools to understand amyloid-mediated neurodegeneration. In my opinion, these insights may further facilitate the development of more precise and effective therapeutic strategies, involving the modulation of crucial players in cellular signaling pathways or membrane

trafficking processes [111–113]. Ongoing research has developed our understanding of how amyloids, particularly Aβ, affect vesicular transport mechanisms in neurons. At the same time, the roles of vesicles in the propagation of amyloid proteins, oligomers, and fibrils are also confirmed in multiple studies. This crosstalk between amyloids and vesicular transport may provide us with multiple options for the therapeutic targeting for neurodegenerative disorders. One possibility could be identifying pharmacological compounds that can modulate the interaction between the vesicular transport system and amyloid proteins. More effective strategies need to be developed to target amyloidogenic pathways and prevent the progression of neurodegeneration. These strategies may include targeting APP processing to lower the production of Aβ or enhance Aβ clearance mechanisms. An overall reduction in amyloid burden may indirectly mitigate the disruption caused by amyloid aggregates to the overall integrity of the neuronal transport system and hence will maintain proper trafficking and delivery of cargoes.

9. Discussion

Amyloids are one of the most highly structured protein forms that have been studied for both pathological and beneficial roles. However, the majority of amyloidogenic proteins are associated with one or multiple disorders, combinedly referred to as proteinopathies. Neuronal death is one of the outcomes of amyloid formation in brain tissues. In recent years, studies have shown that the propagation of amyloids is positively affected by the vesicular transport system. Interestingly, amyloids once formed may affect membrane integrity and disrupt the vesicular transport system also. The crosstalk between amyloids and the vesicular system is an interesting area that needs more attention. This article provides a brief outline of how these two are intertwined. Investigating this relationship may provide better understanding of the early stages of amyloid formation and their propagation, hence may contribute to developing better therapeutic solutions.

Funding: The author wants to thank the Indian Institute of Technology (IIT) Bhilai for supporting his work with Research Initiation Grant ((IITBH/R&D/2024-25/386).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The author declares no conflicts of interest.

References

1. Pearson, H.A.; Peers, C. Physiological roles for amyloid β peptides. *J. Physiol.* **2006**, *575*, 5–10. [CrossRef] [PubMed]
2. Murphy, M.P.; LeVine, H., III. Alzheimer's disease and the amyloid-beta peptide. *J. Alzheimer's Dis.* **2010**, *19*, 311–323. [CrossRef] [PubMed]
3. Cai, W.; Li, L.; Sang, S.; Pan, X.; Zhong, C. Physiological Roles of β-amyloid in Regulating Synaptic Function: Implications for AD Pathophysiology. *Neurosci. Bull.* **2023**, *39*, 1289–1308. [CrossRef] [PubMed]
4. Koo, E.H.; Sisodia, S.S.; Archer, D.R.; Martin, L.J.; Weidemann, A.; Beyreuther, K.; Fischer, P.; Masters, C.L.; Price, D.L. Precursor of amyloid protein in Alzheimer disease undergoes fast anterograde axonal transport. *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 1561–1565. [CrossRef]
5. Marsh, J.; Alifragis, P. Synaptic dysfunction in Alzheimer's disease: The effects of amyloid beta on synaptic vesicle dynamics as a novel target for therapeutic intervention. *Neural Regen. Res.* **2018**, *13*, 616–623. [CrossRef]
6. Decker, H.; Lo, K.Y.; Unger, S.M.; Ferreira, S.T.; Silverman, M.A. Amyloid-beta peptide oligomers disrupt axonal transport through an NMDA receptor-dependent mechanism that is mediated by glycogen synthase kinase 3beta in primary cultured hippocampal neurons. *J. Neurosci.* **2010**, *30*, 9166–9171. [CrossRef]
7. Gan, K.J.; Akram, A.; Blasius, T.L.; Ramser, E.M.; Budaitis, B.G.; Gabrych, D.R.; Verhey, K.J.; Silverman, M.A. GSK3β Impairs KIF1A Transport in a Cellular Model of Alzheimer's Disease but Does Not Regulate Motor Motility at S402. *eNeuro* **2020**, *7*, 0176-20. [CrossRef]
8. Canevari, L.; Abramov, A.Y.; Duchen, M.R. Toxicity of Amyloid β Peptide: Tales of Calcium, Mitochondria, and Oxidative Stress. *Neurochem. Res.* **2004**, *29*, 637–650. [CrossRef]

9. Zhang, L.; Trushin, S.; Christensen, T.A.; Tripathi, U.; Hong, C.; Geroux, R.E.; Howell, K.G.; Poduslo, J.F.; Trushina, E. Differential effect of amyloid beta peptides on mitochondrial axonal trafficking depends on their state of aggregation and binding to the plasma membrane. *Neurobiol. Dis.* **2018**, *114*, 1–16. [CrossRef]
10. Liu, Y.; Peterson, D.A.; Schubert, D. Amyloid β peptide alters intracellular vesicle trafficking and cholesterol homeostasis. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 13266–13271. [CrossRef]
11. Gan, K.J.; Silverman, M.A. Dendritic and axonal mechanisms of Ca^{2+} elevation impair BDNF transport in Aβ oligomer-treated hippocampal neurons. *Mol. Biol. Cell* **2015**, *26*, 1058–1071. [CrossRef] [PubMed]
12. Seifert, B.; Eckenstaler, R.; Rönicke, R.; Leschik, J.; Lutz, B.; Reymann, K.; Lessmann, V.; Brigadski, T. Amyloid-Beta Induced Changes in Vesicular Transport of BDNF in Hippocampal Neurons. *Neural Plast.* **2016**, *2016*, 4145708. [CrossRef] [PubMed]
13. Tan, J.Z.A.; Gleeson, P.A. The role of membrane trafficking in the processing of amyloid precursor protein and production of amyloid peptides in Alzheimer's disease. *Biochim. Biophys. Acta Biomembr.* **2019**, *1861*, 697–712. [CrossRef] [PubMed]
14. Muresan, V.; Ladescu Muresan, Z. Amyloid-β precursor protein: Multiple fragments, numerous transport routes and mechanisms. *Exp. Cell Res.* **2015**, *334*, 45–53. [CrossRef]
15. Coleman, B.M.; Hill, A.F. Extracellular vesicles—Their role in the packaging and spread of misfolded proteins associated with neurodegenerative diseases. *Semin. Cell Dev. Biol.* **2015**, *40*, 89–96. [CrossRef]
16. Zheng, T.; Pu, J.; Chen, Y.; Mao, Y.; Guo, Z.; Pan, H.; Zhang, L.; Zhang, H.; Sun, B.; Zhang, B. Plasma exosomes spread and cluster around β-amyloid plaques in an animal model of Alzheimer's disease. *Front. Aging Neurosci.* **2017**, *9*, 12. [CrossRef]
17. Burwinkel, M.; Lutzenberger, M.; Heppner, F.L.; Schulz-Schaeffer, W.; Baier, M. Intravenous injection of beta-amyloid seeds promotes cerebral amyloid angiopathy (CAA). *Acta Neuropathol. Commun.* **2018**, *6*, 23. [CrossRef]
18. Cintron, A.F.; Dalal, N.V.; Dooyema, J.; Betarbet, R.; Walker, L.C. Transport of cargo from periphery to brain by circulating monocytes. *Brain Res.* **2015**, *1622*, 328–338. [CrossRef]
19. Olsson, T.T.; Klementieva, O.; Gouras, G.K. Prion-like seeding and nucleation of intracellular amyloid-β. *Neurobiol. Dis.* **2018**, *113*, 1–10. [CrossRef]
20. Walker, L.C.; Schelle, J.; Jucker, M. The Prion-Like Properties of Amyloid-β Assemblies: Implications for Alzheimer's Disease. *Cold Spring Harb. Perspect. Med.* **2016**, *6*, a024398. [CrossRef]
21. Lewis, P.A. Vesicular dysfunction and pathways to neurodegeneration. *Essays Biochem.* **2021**, *65*, 941–948. [CrossRef] [PubMed]
22. Upadhyay, A. Structure of proteins: Evolution with unsolved mysteries. *Prog. Biophys. Mol. Biol.* **2019**, *149*, 160–172. [CrossRef] [PubMed]
23. Labbadia, J.; Morimoto, R.I. The biology of proteostasis in aging and disease. *Annu. Rev. Biochem.* **2015**, *84*, 435–464. [CrossRef] [PubMed]
24. Shastry, B.S. Neurodegenerative disorders of protein aggregation. *Neurochem. Int.* **2003**, *43*, 1–7. [CrossRef]
25. Sundaria, N.; Upadhyay, A.; Prasad, A.; Prajapati, V.K.; Poluri, K.M.; Mishra, A. Neurodegeneration & imperfect ageing: Technological limitations and challenges? *Mech. Ageing Dev.* **2021**, *200*, 111574. [CrossRef]
26. Upadhyay, A.; Sundaria, N.; Dhiman, R.; Prajapati, V.K.; Prasad, A.; Mishra, A. Complex Inclusion Bodies and Defective Proteome Hubs in Neurodegenerative Disease: New Clues, New Challenges. *Neuroscientist* **2022**, *28*, 271–282. [CrossRef]
27. Upadhyay, A.; Mishra, A. Amyloids of multiple species: Are they helpful in survival? *Biol. Rev.* **2018**, *93*, 1363–1386. [CrossRef]
28. Scheres, S.H.W.; Ryskeldi-Falcon, B.; Goedert, M. Molecular pathology of neurodegenerative diseases by cryo-EM of amyloids. *Nature* **2023**, *621*, 701–710. [CrossRef]
29. Höhn, A.; Weber, D.; Jung, T.; Ott, C.; Hugo, M.; Kochlik, B.; Kehm, R.; König, J.; Grune, T.; Castro, J.P. Happily (n)ever after: Aging in the context of oxidative stress, proteostasis loss and cellular senescence. *Redox Biol.* **2017**, *11*, 482–501. [CrossRef]
30. Munishkina, L.A.; Ahmad, A.; Fink, A.L.; Uversky, V.N. Guiding protein aggregation with macromolecular crowding. *Biochemistry* **2008**, *47*, 8993–9006. [CrossRef]
31. Minton, A.P. Implications of macromolecular crowding for protein assembly. *Curr. Opin. Struct. Biol.* **2000**, *10*, 34–39. [CrossRef] [PubMed]
32. Gupta, R.; Sahu, M.; Srivastava, D.; Tiwari, S.; Ambasta, R.K.; Kumar, P. Post-translational modifications: Regulators of neurodegenerative proteinopathies. *Ageing Res. Rev.* **2021**, *68*, 101336. [CrossRef] [PubMed]
33. Buxbaum, E. Vesicular Transport in Eukaryotic Cells. In *Fundamentals of Protein Structure and Function*; Buxbaum, E., Ed.; Springer International Publishing: Cham, Switzerland, 2015; pp. 393–420.
34. Barr, F. Vesicular transport. *Essays Biochem.* **2000**, *36*, 37–46. [CrossRef] [PubMed]
35. Nickel, W.; Brügger, B.; Wieland, F.T. Vesicular transport: The core machinery of COPI recruitment and budding. *J. Cell Sci.* **2002**, *115*, 3235–3240. [CrossRef]
36. Alberts, B.; Johnson, A.; Lewis, J.; Raff, M.; Roberts, K.; Walter, P. The molecular mechanisms of membrane transport and the maintenance of compartmental diversity. In *Molecular Biology of the Cell*, 4th ed.; Garland Science: New York, NY, USA, 2002.
37. Schmid, S.L. Clathrin-Coated Vesicle Formation and Protein Sorting: An Integrated Process. *Annu. Rev. Biochem.* **1997**, *66*, 511–548. [CrossRef]
38. Paraan, M.; Mendez, J.; Sharum, S.; Kurtin, D.; He, H.; Stagg, S.M. The structures of natively assembled clathrin-coated vesicles. *Sci. Adv.* **2020**, *6*, eaba8397. [CrossRef]

39. Pigino, G.; Morfini, G.A.; Brady, S.T. Chapter 7—Intracellular Trafficking. In *Basic Neurochemistry*, 8th ed.; Brady, S.T., Siegel, G.J., Albers, R.W., Price, D.L., Eds.; Academic Press: New York, NY, USA, 2012; pp. 119–145.
40. Bonifacino, J.S.; Glick, B.S. The Mechanisms of Vesicle Budding and Fusion. *Cell* **2004**, *116*, 153–166. [CrossRef]
41. Jahn, R.; Cafiso, D.C.; Tamm, L.K. Mechanisms of SNARE proteins in membrane fusion. *Nat. Rev. Mol. Cell Biol.* **2024**, *25*, 101–118. [CrossRef]
42. Palfreyman, M.T.; West, S.E.; Jorgensen, E.M. SNARE Proteins in Synaptic Vesicle Fusion. *Adv. Neurobiol.* **2023**, *33*, 63–118. [CrossRef]
43. Pérez-González, R.; Kim, Y.; Miller, C.; Pacheco-Quinto, J.; Eckman, E.A.; Levy, E. Extracellular vesicles: Where the amyloid precursor protein carboxyl-terminal fragments accumulate and amyloid-β oligomerizes. *FASEB J.* **2020**, *34*, 12922–12931. [CrossRef]
44. Osborne, O.M.; Kowalczyk, J.M.; Louis, K.D.P.; Daftari, M.T.; Colbert, B.M.; Naranjo, O.; Torices, S.; András, I.E.; Dykxhoorn, D.M.; Toborek, M. Brain endothelium-derived extracellular vesicles containing amyloid-beta induce mitochondrial alterations in neural progenitor cells. *Extracell. Vesicles Circ. Nucleic Acids* **2022**, *3*, 340–362. [CrossRef]
45. Das, A.K.; Pandit, R.; Maiti, S. Effect of amyloids on the vesicular machinery: Implications for somatic neurotransmission. *Philos. Trans. R. Soc. B Biol. Sci.* **2015**, *370*, 20140187. [CrossRef] [PubMed]
46. McLaurin, J.; Chakrabartty, A. Membrane Disruption by Alzheimer β-Amyloid Peptides Mediated through Specific Binding to Either Phospholipids or Gangliosides: Implications for Neurotoxicity. *J. Biol. Chem.* **1996**, *271*, 26482–26489. [CrossRef]
47. Dietschy, J.M.; Turley, S.D. Thematic review series: Brain Lipids. Cholesterol metabolism in the central nervous system during early development and in the mature animal. *J. Lipid Res.* **2004**, *45*, 1375–1397. [CrossRef]
48. Rudajev, V.; Novotny, J. Cholesterol as a key player in amyloid β-mediated toxicity in Alzheimer's disease. *Front. Mol. Neurosci.* **2022**, *15*, 937056. [CrossRef] [PubMed]
49. Berman, D.E.; Dall'Armi, C.; Voronov, S.V.; McIntire, L.B.J.; Zhang, H.; Moore, A.Z.; Staniszewski, A.; Arancio, O.; Kim, T.-W.; Di Paolo, G. Oligomeric amyloid-β peptide disrupts phosphatidylinositol-4,5-bisphosphate metabolism. *Nat. Neurosci.* **2008**, *11*, 547–554. [CrossRef] [PubMed]
50. Kelly, B.L.; Ferreira, A. Beta-amyloid disrupted synaptic vesicle endocytosis in cultured hippocampal neurons. *Neuroscience* **2007**, *147*, 60–70. [CrossRef] [PubMed]
51. Bathina, S.; Das, U.N. Brain-derived neurotrophic factor and its clinical implications. *Arch. Med. Sci* **2015**, *11*, 1164–1178. [CrossRef]
52. Poon, W.W.; Carlos, A.J.; Aguilar, B.L.; Berchtold, N.C.; Kawano, C.K.; Zograbyan, V.; Yaopruke, T.; Shelanski, M.; Cotman, C.W. β-Amyloid (Aβ) oligomers impair brain-derived neurotrophic factor retrograde trafficking by down-regulating ubiquitin C-terminal hydrolase, UCH-L1. *J. Biol. Chem.* **2013**, *288*, 16937–16948. [CrossRef]
53. Poon, W.W.; Blurton-Jones, M.; Tu, C.H.; Feinberg, L.M.; Chabrier, M.A.; Harris, J.W.; Jeon, N.L.; Cotman, C.W. β-Amyloid impairs axonal BDNF retrograde trafficking. *Neurobiol. Aging* **2011**, *32*, 821–833. [CrossRef]
54. Eggert, S.; Kins, S.; Endres, K.; Brigadski, T. Brothers in arms: proBDNF/BDNF and sAPPα/Aβ-signaling and their common interplay with ADAM10, TrkB, p75NTR, sortilin, and sorLA in the progression of Alzheimer's disease. *Biol. Chem.* **2022**, *403*, 43–71. [CrossRef] [PubMed]
55. Icking, A.; Amaddii, M.; Ruonala, M.; Höning, S.; Tikkanen, R. Polarized transport of Alzheimer amyloid precursor protein is mediated by adaptor protein complex AP1-1B. *Traffic* **2007**, *8*, 285–296. [CrossRef] [PubMed]
56. de Wilde, M.C.; Overk, C.R.; Sijben, J.W.; Masliah, E. Meta-analysis of synaptic pathology in Alzheimer's disease reveals selective molecular vesicular machinery vulnerability. *Alzheimer's Dement.* **2016**, *12*, 633–644. [CrossRef] [PubMed]
57. Greten-Harrison, B.; Polydoro, M.; Morimoto-Tomita, M.; Diao, L.; Williams, A.M.; Nie, E.H.; Makani, S.; Tian, N.; Castillo, P.E.; Buchman, V.L.; et al. αβγ-Synuclein triple knockout mice reveal age-dependent neuronal dysfunction. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 19573–19578. [CrossRef]
58. Smith, R.; Bacos, K.; Fedele, V.; Soulet, D.; Walz, H.A.; Obermüller, S.; Lindqvist, A.; Björkqvist, M.; Klein, P.; Önnerfjord, P.; et al. Mutant huntingtin interacts with β-tubulin and disrupts vesicular transport and insulin secretion. *Hum. Mol. Genet.* **2009**, *18*, 3942–3954. [CrossRef]
59. Zeineddine, R.; Pundavela, J.F.; Corcoran, L.; Stewart, E.M.; Do-Ha, D.; Bax, M.; Guillemin, G.; Vine, K.L.; Hatters, D.M.; Ecroyd, H.; et al. SOD1 protein aggregates stimulate macropinocytosis in neurons to facilitate their propagation. *Mol. Neurodegener.* **2015**, *10*, 57. [CrossRef]
60. Wang, L.; Das, U.; Scott, D.A.; Tang, Y.; McLean, P.J.; Roy, S. α-Synuclein Multimers Cluster Synaptic Vesicles and Attenuate Recycling. *Curr. Biol.* **2014**, *24*, 2319–2326. [CrossRef]
61. Jani, R.A.; Setty, S.R.G. Membrane trafficking and vesicle fusion: Post-Palade era researchers win the Nobel Prize. *Resonance* **2014**, *19*, 421–445. [CrossRef]
62. Bodart-Santos, V.; Pinheiro, L.S.; da Silva-Junior, A.J.; Froza, R.L.; Ahrens, R.; Gonçalves, R.A.; Andrade, M.M.; Chen, Y.; Alcantara, C.d.L.; Grinberg, L.T.; et al. Alzheimer's disease brain-derived extracellular vesicles reveal altered synapse-related proteome and induce cognitive impairment in mice. *Alzheimer's Dement.* **2023**, *19*, 5418–5436. [CrossRef]
63. Rui, Y.; Zheng, J.Q. Amyloid β oligomers elicit mitochondrial transport defects and fragmentation in a time-dependent and pathway-specific manner. *Mol. Brain* **2016**, *9*, 79. [CrossRef]

64. Schindowski, K.; Belarbi, K.; Buée, L. Neurotrophic factors in Alzheimer's disease: Role of axonal transport. *Genes Brain Behav.* **2008**, *7* (Suppl. S1), 43–56. [CrossRef] [PubMed]
65. Haass, C.; Kaether, C.; Thinakaran, G.; Sisodia, S. Trafficking and proteolytic processing of APP. *Cold Spring Harb. Perspect. Med.* **2012**, *2*, a006270. [CrossRef] [PubMed]
66. Upadhyay, A.; Chhangani, D.; Rao, N.R.; Kofler, J.; Vassar, R.; Rincon-Limas, D.E.; Savas, J.N. Amyloid fibril proteomics of AD brains reveals modifiers of aggregation and toxicity. *Mol. Neurodegener.* **2023**, *18*, 61. [CrossRef] [PubMed]
67. Sengupta, U.; Nilson, A.N.; Kayed, R. The Role of Amyloid-β Oligomers in Toxicity, Propagation, and Immunotherapy. *eBioMedicine* **2016**, *6*, 42–49. [CrossRef] [PubMed]
68. Shankar, G.M.; Li, S.; Mehta, T.H.; Garcia-Munoz, A.; Shepardson, N.E.; Smith, I.; Brett, F.M.; Farrell, M.A.; Rowan, M.J.; Lemere, C.A.; et al. Amyloid-β protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nat. Med.* **2008**, *14*, 837–842. [CrossRef]
69. Lambert, M.P.; Barlow, A.K.; Chromy, B.A.; Edwards, C.; Freed, R.; Liosatos, M.; Morgan, T.E.; Rozovsky, I.; Trommer, B.; Viola, K.L.; et al. Diffusible, nonfibrillar ligands derived from Aβ $_{1–42}$ are potent central nervous system neurotoxins. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 6448–6453. [CrossRef]
70. Koffie, R.M.; Meyer-Luehmann, M.; Hashimoto, T.; Adams, K.W.; Mielke, M.L.; Garcia-Alloza, M.; Micheva, K.D.; Smith, S.J.; Kim, M.L.; Lee, V.M.; et al. Oligomeric amyloid β associates with postsynaptic densities and correlates with excitatory synapse loss near senile plaques. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 4012–4017. [CrossRef]
71. Meyer-Luehmann, M.; Spires-Jones, T.L.; Prada, C.; Garcia-Alloza, M.; de Calignon, A.; Rozkalne, A.; Koenigsknecht-Talboo, J.; Holtzman, D.M.; Bacskai, B.J.; Hyman, B.T. Rapid appearance and local toxicity of amyloid-β plaques in a mouse model of Alzheimer's disease. *Nature* **2008**, *451*, 720–724. [CrossRef]
72. Shah, P.; Lal, N.; Leung, E.; Traul, D.E.; Gonzalo-Ruiz, A.; Geula, C. Neuronal and axonal loss are selectively linked to fibrillar amyloid-{beta} within plaques of the aged primate cerebral cortex. *Am. J. Pathol.* **2010**, *177*, 325–333. [CrossRef]
73. Ricciarelli, R.; Fedele, E. The Amyloid Cascade Hypothesis in Alzheimer's Disease: It's Time to Change Our Mind. *Curr. Neuropharmacol.* **2017**, *15*, 926–935. [CrossRef]
74. Hardy, J.; Selkoe, D.J. The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science* **2002**, *297*, 353–356. [CrossRef] [PubMed]
75. Grothe, M.J.; Barthel, H.; Sepulcre, J.; Dyrba, M.; Sabri, O.; Teipel, S.J. In vivo staging of regional amyloid deposition. *Neurology* **2017**, *89*, 2031–2038. [CrossRef] [PubMed]
76. Serrano-Pozo, A.; Frosch, M.P.; Masliah, E.; Hyman, B.T. Neuropathological alterations in Alzheimer disease. *Cold Spring Harb. Perspect. Med.* **2011**, *1*, a006189. [CrossRef] [PubMed]
77. Thal, D.R.; Rüb, U.; Orantes, M.; Braak, H. Phases of Aβ-deposition in the human brain and its relevance for the development of AD. *Neurology* **2002**, *58*, 1791–1800. [CrossRef]
78. Watts, J.C.; Prusiner, S.B. β-Amyloid Prions and the Pathobiology of Alzheimer's Disease. *Cold Spring Harb. Perspect. Med.* **2018**, *8*, a023507. [CrossRef]
79. Sinha, A.; Principe, S.; Alfaro, J.; Ignatchenko, A.; Ignatchenko, V.; Kislinger, T. Proteomic Profiling of Secreted Proteins, Exosomes, and Microvesicles in Cell Culture Conditioned Media. *Methods Mol. Biol.* **2018**, *1722*, 91–102. [CrossRef]
80. Meyer-Luehmann, M.; Stalder, M.; Herzig, M.C.; Kaeser, S.A.; Kohler, E.; Pfeifer, M.; Boncristiano, S.; Mathews, P.M.; Mercken, M.; Abramowski, D.; et al. Extracellular amyloid formation and associated pathology in neural grafts. *Nat. Neurosci.* **2003**, *6*, 370–377. [CrossRef]
81. Eisele, Y.S.; Obermüller, U.; Heilbronner, G.; Baumann, F.; Kaeser, S.A.; Wolburg, H.; Walker, L.C.; Staufenbiel, M.; Heikenwalder, M.; Jucker, M. Peripherally applied Abeta-containing inoculates induce cerebral beta-amyloidosis. *Science* **2010**, *330*, 980–982. [CrossRef]
82. Sharples, R.A.; Vella, L.J.; Nisbet, R.M.; Naylor, R.; Perez, K.; Barnham, K.J.; Masters, C.L.; Hill, A.F. Inhibition of gamma-secretase causes increased secretion of amyloid precursor protein C-terminal fragments in association with exosomes. *FASEB J.* **2008**, *22*, 1469–1478. [CrossRef]
83. Rajendran, L.; Honsho, M.; Zahn, T.R.; Keller, P.; Geiger, K.D.; Verkade, P.; Simons, K. Alzheimer's disease beta-amyloid peptides are released in association with exosomes. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 11172–11177. [CrossRef]
84. Falcicchia, C.; Tozzi, F.; Gabrielli, M.; Amoretti, S.; Masini, G.; Nardi, G.; Guglielmo, S.; Ratto, G.M.; Arancio, O.; Verderio, C.; et al. Microglial extracellular vesicles induce Alzheimer's disease-related cortico-hippocampal network dysfunction. *Brain Commun.* **2023**, *5*, fcad170. [CrossRef] [PubMed]
85. Zheng, T.; Wu, X.; Wei, X.; Wang, M.; Zhang, B. The release and transmission of amyloid precursor protein via exosomes. *Neurochem. Int.* **2018**, *114*, 18–25. [CrossRef] [PubMed]
86. Yamaguchi, H.; Kawahara, H.; Kodera, N.; Kumaki, A.; Tada, Y.; Tang, Z.; Sakai, K.; Ono, K.; Yamada, M.; Hanayama, R. Extracellular vesicles contribute to the metabolism of transthyretin amyloid in hereditary transthyretin amyloidosis. *Front. Mol. Biosci.* **2022**, *9*, 839917. [CrossRef] [PubMed]
87. Halipi, V.; Sasanian, N.; Feng, J.; Hu, J.; Lubart, Q.; Bernson, D.; van Leeuwen, D.; Ahmadpour, D.; Sparr, E.; Esbjörner, E.K. Extracellular Vesicles Slow Down Aβ(1–42) Aggregation by Interfering with the Amyloid Fibril Elongation Step. *ACS Chem. Neurosci.* **2024**, *15*, 944–954. [CrossRef] [PubMed]

88. Gabrielli, M.; Tozzi, F.; Verderio, C.; Origlia, N. Emerging Roles of Extracellular Vesicles in Alzheimer's Disease: Focus on Synaptic Dysfunction and Vesicle–Neuron Interaction. *Cells* **2023**, *12*, 63. [CrossRef]
89. Perez-Gonzalez, R.; Gauthier, S.A.; Kumar, A.; Levy, E. The exosome secretory pathway transports amyloid precursor protein carboxyl-terminal fragments from the cell into the brain extracellular space. *J. Biol. Chem.* **2012**, *287*, 43108–43115. [CrossRef]
90. Zhao, Y.; Gu, Y.; Zhang, Q.; Liu, H.; Liu, Y. The Potential Roles of Exosomes Carrying APP and Tau Cleavage Products in Alzheimer's Disease. *J. Clin. Med.* **2023**, *12*, 1883. [CrossRef]
91. Takeuchi, S.; Ueda, N.; Suzuki, K.; Shimozawa, N.; Yasutomi, Y.; Kimura, N. Elevated Membrane Cholesterol Disrupts Lysosomal Degradation to Induce β-Amyloid Accumulation: The Potential Mechanism Underlying Augmentation of β-Amyloid Pathology by Type 2 Diabetes Mellitus. *Am. J. Pathol.* **2019**, *189*, 391–404. [CrossRef]
92. Burrinha, T.; Martinsson, I.; Gomes, R.; Terrasso, A.P.; Gouras, G.K.; Almeida, C.G. Upregulation of APP endocytosis by neuronal aging drives amyloid-dependent synapse loss. *J. Cell Sci.* **2021**, *134*, jcs255752. [CrossRef]
93. Liu, L.; Drouet, V.; Wu, J.W.; Witter, M.P.; Small, S.A.; Clelland, C.; Duff, K. Trans-Synaptic Spread of Tau Pathology In Vivo. *PLoS ONE* **2012**, *7*, e31302. [CrossRef]
94. Jucker, M.; Walker, L.C. Pathogenic protein seeding in Alzheimer disease and other neurodegenerative disorders. *Ann. Neurol.* **2011**, *70*, 532–540. [CrossRef] [PubMed]
95. Clavaguera, F.; Bolmont, T.; Crowther, R.A.; Abramowski, D.; Frank, S.; Probst, A.; Fraser, G.; Stalder, A.K.; Beibel, M.; Staufenbiel, M. Transmission and spreading of tauopathy in transgenic mouse brain. *Nat. Cell Biol.* **2009**, *11*, 909–913. [CrossRef] [PubMed]
96. Clavaguera, F.; Akatsu, H.; Fraser, G.; Crowther, R.A.; Frank, S.; Hench, J.; Probst, A.; Winkler, D.T.; Reichwald, J.; Staufenbiel, M. Brain homogenates from human tauopathies induce tau inclusions in mouse brain. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 9535–9540. [CrossRef] [PubMed]
97. Lasagna-Reeves, C.A.; Castillo-Carranza, D.L.; Sengupta, U.; Guerrero-Munoz, M.J.; Kiritoshi, T.; Neugebauer, V.; Jackson, G.R.; Kayed, R. Alzheimer brain-derived tau oligomers propagate pathology from endogenous tau. *Sci. Rep.* **2012**, *2*, 700. [CrossRef]
98. Smolek, T.; Jadhav, S.; Brezovakova, V.; Cubinkova, V.; Valachova, B.; Novak, P.; Zilka, N. First-in-rat study of human Alzheimer's disease tau propagation. *Mol. Neurobiol.* **2019**, *56*, 621–631. [CrossRef]
99. Iba, M.; Guo, J.L.; McBride, J.D.; Zhang, B.; Trojanowski, J.Q.; Lee, V.M.-Y. Synthetic tau fibrils mediate transmission of neurofibrillary tangles in a transgenic mouse model of Alzheimer's-like tauopathy. *J. Neurosci.* **2013**, *33*, 1024–1037. [CrossRef]
100. Guo, J.L.; Lee, V.M. Neurofibrillary tangle-like tau pathology induced by synthetic tau fibrils in primary neurons over-expressing mutant tau. *FEBS Lett.* **2013**, *587*, 717–723. [CrossRef]
101. Frost, B.; Jacks, R.L.; Diamond, M.I. Propagation of tau misfolding from the outside to the inside of a cell. *J. Biol. Chem.* **2009**, *284*, 12845–12852. [CrossRef]
102. Calafate, S.; Buist, A.; Miskiewicz, K.; Vijayan, V.; Daneels, G.; de Strooper, B.; de Wit, J.; Verstreken, P.; Moechars, D. Synaptic contacts enhance cell-to-cell tau pathology propagation. *Cell Rep.* **2015**, *11*, 1176–1183. [CrossRef]
103. Baker, S.; Polanco, J.C.; Götz, J. Extracellular vesicles containing P301L mutant tau accelerate pathological tau phosphorylation and oligomer formation but do not seed mature neurofibrillary tangles in ALZ17 mice. *J. Alzheimer's Dis.* **2016**, *54*, 1207–1217. [CrossRef]
104. Polanco, J.C.; Scicluna, B.J.; Hill, A.F.; Götz, J. Extracellular vesicles isolated from the brains of rTg4510 mice seed tau protein aggregation in a threshold-dependent manner. *J. Biol. Chem.* **2016**, *291*, 12445–12466. [CrossRef] [PubMed]
105. Fiandaca, M.S.; Kapogiannis, D.; Mapstone, M.; Boxer, A.; Eitan, E.; Schwartz, J.B.; Abner, E.L.; Petersen, R.C.; Federoff, H.J.; Miller, B.L. Identification of preclinical Alzheimer's disease by a profile of pathogenic proteins in neurally derived blood exosomes: A case-control study. *Alzheimer's Dement.* **2015**, *11*, 600–607.e601. [CrossRef] [PubMed]
106. Saman, S.; Kim, W.; Raya, M.; Visnick, Y.; Miro, S.; Saman, S.; Jackson, B.; McKee, A.C.; Alvarez, V.E.; Lee, N.C. Exosome-associated tau is secreted in tauopathy models and is selectively phosphorylated in cerebrospinal fluid in early Alzheimer disease. *J. Biol. Chem.* **2012**, *287*, 3842–3849. [CrossRef] [PubMed]
107. Dujardin, S.; Bégard, S.; Caillierez, R.; Lachaud, C.; Delattre, L.; Carrier, S.; Loyens, A.; Galas, M.-C.; Bousset, L.; Melki, R. Ectosomes: A new mechanism for non-exosomal secretion of tau protein. *PLoS ONE* **2014**, *9*, e100760. [CrossRef] [PubMed]
108. Lasagna-Reeves, C.A.; Sengupta, U.; Castillo-Carranza, D.; Gerson, J.E.; Guerrero-Munoz, M.; Troncoso, J.C.; Jackson, G.R.; Kayed, R. The formation of tau pore-like structures is prevalent and cell specific: Possible implications for the disease phenotypes. *Acta Neuropathol. Commun.* **2014**, *2*, 56. [CrossRef]
109. Merezhko, M.; Brunello, C.A.; Yan, X.; Vihinen, H.; Jokitalo, E.; Uronen, R.-L.; Huttunen, H.J. Secretion of Tau via an Unconventional Non-vesicular Mechanism. *Cell Rep.* **2018**, *25*, 2027–2035.e24. [CrossRef]
110. Patel, N.; Ramachandran, S.; Azimov, R.; Kagan, B.L.; Lal, R. Ion Channel Formation by Tau Protein: Implications for Alzheimer's Disease and Tauopathies. *Biochemistry* **2015**, *54*, 7320–7325. [CrossRef]
111. Kumar, M.A.; Baba, S.K.; Sadida, H.Q.; Marzooqi, S.A.; Jerobin, J.; Altemani, F.H.; Algehainy, N.; Alanazi, M.A.; Abou-Samra, A.-B.; Kumar, R.; et al. Extracellular vesicles as tools and targets in therapy for diseases. *Signal Transduct. Target. Ther.* **2024**, *9*, 27. [CrossRef]

112. Soliman, H.M.; Ghonaim, G.A.; Gharib, S.M.; Chopra, H.; Farag, A.K.; Hassanin, M.H.; Nagah, A.; Emad-Eldin, M.; Hashem, N.E.; Yahya, G.; et al. Exosomes in Alzheimer's Disease: From Being Pathological Players to Potential Diagnostics and Therapeutics. *Int. J. Mol. Sci.* **2021**, *22*, 10794. [CrossRef]
113. Cui, L.; Li, H.; Xi, Y.; Hu, Q.; Liu, H.; Fan, J.; Xiang, Y.; Zhang, X.; Shui, W.; Lai, Y. Vesicle trafficking and vesicle fusion: Mechanisms, biological functions, and their implications for potential disease therapy. *Mol. Biomed.* **2022**, *3*, 29. [CrossRef]