IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
May 2018 Vol.:12, Issue:2

Role of Dynein in Alzheimer Disease

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submission: 20 April 2018
Accepted: 27 April 2018
Published: 31 May 2018

Keywords: Dynein, Alzheimer's disease, cognitive impairment, plaques.

ABSTRACT

Alzheimer's disease (AD) is characterized by the accumulation of proteins in the brain in the form of plaques and tangles and associated cognitive impairment. Various studies have shown that the number of motor proteins is involved in the neurodegenerative progression of the AD. In the AD the dyneins is a precise protein for thinking. The dyneins are a subfamily of the AAA+ (ATPases Associated with diverse cellular Activities) proteins. Two general forms of dynein are found in eukaryotes i.e. Cytoplasmic dynein and axonal dynein. In Alzheimer, the axonal dynein is focusing and dysfunction of this protein leads to various diseases. In this review, we have critically discussed the possible mechanisms involved in the modulation of dynein in Alzheimer conditions.

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INTRODUCTION

Alzheimer's disease (AD) is an incurable and progressive disease characterized by the deposition of proteins in the brain in the form of plaques and tangles and associated cognitive impairment. The AD is the most common cause of dementia in the elderly population. As there is a progressive increase in human longevity and absence of any preventative medicine, the AD is projected to affect 100 million people by 2050. [1]

Population aging has become a worldwide universal phenomenon. The reports from the UN Aging Program and the US Centers for Disease Control and Prevention have projected that the number of older people (65+ years) in the world is expected to increase from 420 million in 2000 to nearly 1 billion by 2030, with the proportion of older people being increased from 7% to 12%. [2,3] Developing countries will see the largest increase in absolute numbers of older persons. Thus, the developing nation's share of the worldwide aging population will increase from 59% to 71%. Because the occurrence of the AD is strongly associated with increasing age, it is anticipated that this dementing disorder will pose huge challenges to public health and elderly care systems in all countries across the world.

There seem to be many correlations between the age-related degenerative conditions of human Alzheimer disease and cognitive dysfunction syndrome in companion animals. [4] In recent years, neurodegenerative diseases have become an important worldwide health issue. These diseases affect the nervous system and share features such as selective neuronal death, protein aggregation, oxidative stress, mitochondrial dysfunction, transition metal accumulation and inflammation. [5,6] In Alzheimer's disease (AD), Parkinson's disease (PD), Huntington disease (HD), prion diseases and frontotemporal dementia (FTD) there is a substantial neuronal loss in at least some regions of the brain and the deposition of misfolded amyloidogenic proteins. [7] Although from several decades it was thought that large protein deposits such as amyloid plaques, tangles, or Lewy bodies are the toxic culprit of these diseases, but also small diffusible and SDS-stable oligomers are now regarded to at least initiate the diseases. [8] AD is a neurodegenerative disorder characterized by the excessive accumulation of extracellular amyloid (Aβ) in senile plaques, intracellular hyperphosphorylated tau aggregates in neurofibrillary tangles (NFTs) and selective cholinergic neuronal loss in the brain regions involved in learning and memory. [9, 10]

A key pathological hallmark for the AD is abnormally hyperphosphorylated tau protein. Tau proteins are a group of microtubule-associated proteins abundant in neuronal cells and play

an important role in microtubules stabilization, axonal transportation, and neurite outgrowth under physiological conditions. [11] In all these disorders there is a strong correlation between cognitive dysfunction and the level of tau intraneuronal aggregates and their localization.[12] One pathological hallmark of tauopathies including AD is an aberrant somatodendritic accumulation of highly phosphorylated tau. [13,14] The autopsy of an AD patient indicates that a huge amount of cell death occurs in different regions of the brain that is associated with the presence of two aberrant structures: senile plaques (SP), composed by the amyloid peptide, and neurofibrillary tangles (NFT), whose main component is tau protein. This is the final picture of the disease, but what happens in the patient's brain that provokes the formation of these aberrant structures and cell death is not properly known. At present, there are some hypotheses that try to explain why neuron dies, and how SP and NFT accumulate in the different types of the AD such as the familial and sporadic types. Although there are differences between these two different types of AD, we will concentrate here on some of the common features.

Neurons are highly vulnerable to functional alterations in microtubule-based motor proteins responsible for the execution of FAT (Fast axonal transport). Genetic evidence supports this contention, as reductions in conventional kinesin and cDyn function resulting from mutations in selected motor subunits which are sufficient to promote degeneration of specific neuronal populations.[15,16] For example, autosomal dominant loss of function mutations in kinesin-1A results in hereditary spastic paraplegia [17], a disease featuring well-documented dying-back degeneration of upper motor neurons.[18] Similarly, mutations in several cDyn subunits, including dynein heavy chain and dynactin result in dying-back degeneration of sensory and/or motor neurons [19] which leads to progression of the AD.

Relevant to this review, pathological studies across a wide spectrum of neurodegenerative diseases indicate that neurons featuring deficits in FAT (Fast Axonal Transport) undergo dying-back degeneration.[20,21] Taken together, these observations clearly indicate that reductions in FAT alone suffice to induce dying-back degeneration of neurons.

DYNEINS

The dyneins are a subfamily of the AAA+ proteins. Two general forms of dynein are found in eukaryotes. The axonemal dyneins are associated with the bundle of microtubules the axoneme comprising the cilium and are responsible for the ciliary beating. The human genome contains 13 forms of axonemal dynein. Surprisingly, this degree of complexity in

large parts the multiplicity of dyneins functioning within a given axoneme, the activities of which are coordinated to produce highly specific Wc waveforms.[22] Cytoplasmic dynein consists of two forms. The major form, also referred to as MAP1C or dynein 1, is ubiquitously expressed.[23,24] In contrast to the axonemal dyneins, this one form of dynein is involved in a very wide range of cellular functions. [25] It associates with diverse membranous organelles, including the Golgi apparatus and components of the endosomal/lysosomal pathway, which it transports toward the microtubule minus end. During the early stages of mitosis, the same form of dynein appears at mitotic kinetochores. Its role is not yet understood, though it may participate in the initial capture of chromosomes by microtubules and in removing checkpoint, proteins at the onset of anaphase. Dynein 1 also appears at the cell cortex, from a site where it is thought to orient the mitotic spindle. In migrating cells, it appears at the leading cell cortex and surrounding the microtubule cytoskeleton, participating in cell steering. At last, dynein 1 has been involved in the transport of diverse macromolecular complexes, including mRNA complexes, centrosomal precursor complexes.

DYNEIN COMPLEXES

Dyneins are a family of ATP-fuelled motor proteins that move toward the minus ends of microtubules.[26] Cytoplasmic dynein transports different intracellular cargoes, generate forces at multiple sites within the cell division machinery, and is implicated in several forms of the neurological disorder.[27] Intraflagellar transport takes place by a closely related dynein.[28] In contrast, axonemal dyneins power the beating of cilia and flagella.[29] Axonemal dynein dysfunctions cause ciliopathies resulting in infertility and improper left-right body asymmetry. To perform their functions, dyneins have a divergent tail domain that specifies distinct cargo-binding and oligomerization properties, attached to a motor domain of 300–400 kDa. High-resolution structural information is available for the motor domain of cytoplasmic dynein.[30,31], building on earlier insights from electron microscopy (EM) and sequence analysis. [32,33] The head domain contains six AAA+ modules, which fold into a ring. The first module (AAA1) is the main site of ATP hydrolysis, whereas AAA2 and AAA3–AAA4 appear to be subsidiary nucleotide binding and hydrolysis sites, respectively. N terminal to AAA1 is a linker domain that connects to the tail. Dynein's microtubule-binding domain lies at the tip of a long coiled-coil stalk that protrudes as an extension from AAA4. The stalk interacts with a second coiled-coil stiffly embedded in AAA5 (also known as the buttress). The microtubule-binding domain and AAA1 are coupled through a long-

range communication pathway [34], allowing dynein to sequentially bind and release its microtubule track during cycles of ATP hydrolysis.

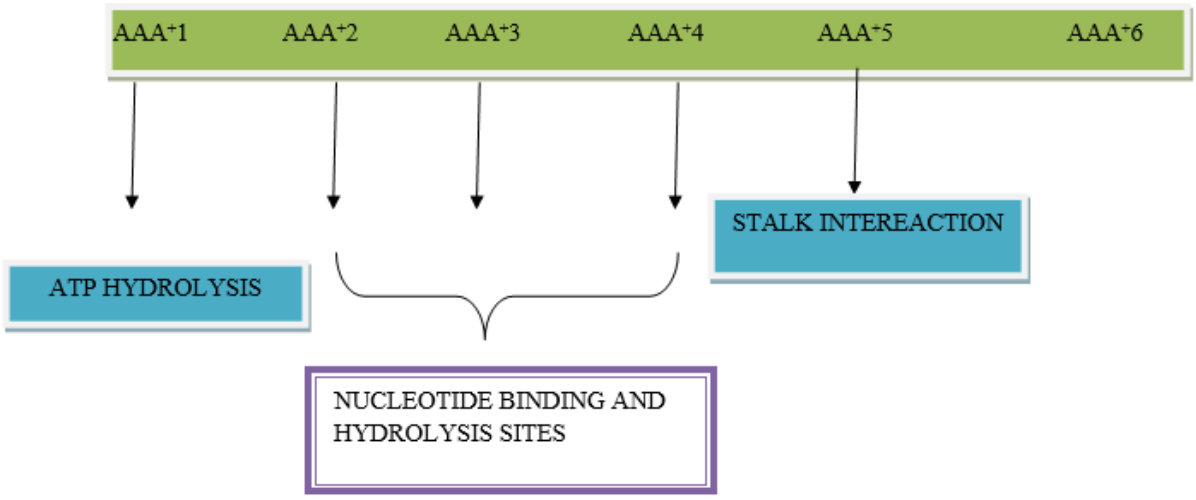

Fig 1. Structural information of dynein

TYPES OF DYNEINS

CYTOPLASMIC DYNEIN

Cytoplasmic dynein, having a molecular mass of about 1.5 Megadaltons (MDa), contains approximately twelve polypeptide subunits: two identical "heavy chains," 520 kDa in mass, which contain the ATPase activity and are thus responsible for generating movement along the microtubule; two 74 kDa intermediate chains which are believed to anchor the dynein to its cargo; four 53-59 kDa intermediate chains and several light chains which are less understood.

The force-generating ATPase activity of each dynein heavy chain is located in its large doughnut-shaped "head", which is related to other AAA proteins, while two projections from the head connect it to other cytoplasmic structures. One projection, the coiled-coil stalk, binds to and "walks" along the surface of the microtubule via a repeated cycle of detachment and reattachment. The other projection, the extended tail binds to the intermediate and light chain subunits which attach the dynein to its cargo. The alternating activity of the paired heavy chains in the complete cytoplasmic dynein motor enables a single dynein molecule to transport its cargo by "walking" a considerable distance along a microtubule without becoming completely detached. In eukaryotes, for activation and regulation of cytoplasmic

dynein, dynactin is required, which is also essential for mitosis. This dynactin possibly facilitates the attachment of dynein to its cargo.

AXONEMAL DYNEIN

Axonemal dynein comes in multiple forms that contain either one, two or three non-identical heavy chains (depending upon the organism and location in the cilium). Each heavy chain has a globular motor domain with a doughnut-shaped structure believed to resemble that of other AAA proteins, a coiled coil "stalk" that binds to the microtubule, and an extended tail (or "stem") that attaches to a neighboring microtubule of the same axoneme. Each dynein molecule thus forms a cross-bridge between two adjacent microtubules of the ciliary axoneme. The AAA ATPase motor domain undergoes a conformational change that causes the microtubule-binding stalk to pivot relative to the cargo-binding tail with the result that one microtubule slides relative to the other [35]. This sliding produces the bending movement needed for cilia to beat and propel the cell or other particles. Groups of dynein molecules responsible for movement in opposite directions are probably activated and inactivated in a coordinated fashion to provide back and forth movement and flagella. The radial spoke has been proposed as the structures that synchronize this movement.

STRUCTURE OF DYNEIN

Dynein represents one of the families of molecular motors that produce directed movement along microtubules. [36] All dyneins travels towards the proximal or minus-ends of microtubules. *In situ*, dynein is a macromolecular complex consisting of large, intermediate and small-sized protein subunits. Intracellular location of the dynein and regulation of its motor activity is specified by intermediate and light chains. The heavy chain consists of the motor machinery which is responsible for the conversion of chemical energy into the directed mechanical force applied to the microtubule surface. Many organisms express multiple dynein heavy chain genes that encode distinct protein isoforms, having four functional classes: (i) axonemal (ciliary or flagellar) outer arm dyneins; (ii) axonemal inner arm dyneins; (iii) non-axonemal (‘cytoplasmic’) dynein-1, also called MAP1C, Dhc1a and Dyh1; and (iv) cytoplasmic dynein-2, also called Dhc1b and Dyh2.[37,38]

Some of the best views of the dynein complex along with head and tail domain were obtained nearly two decades ago.[39] These electron microscopy images showed axonemal outer arm dynein to be a bunches of two or three globular heads joined through short tails; each head-

tail structure formed from a separate heavy chain. Despite its mass, the relatively compact dynein particle is less extended than the other cytoskeletal motors of lower molecular mass. Beginning with the first examples published a decade ago, the complete sequences of approximately twenty dynein heavy chains have been reported. These sequences are derived from a wide variety of organisms and include all four functional classes of dynein. The comparison of these sequences provides glimpses of how the dynein heavy chain folds into the structure seen with the electron microscope. The dynein heavy chain is enormous, being approximately 4600 amino acid residues in length, The most highly divergent portion of the heavy chain sequence is the N-terminal ~1300 residues. This portion of the protein forms the relatively short tail of dynein, and its sequence is best correlated with the functional class of the dynein isoform. [40,41] Interactions within the N-terminal domain are important for heavy chain dimerization [42,43] and the binding of accessory proteins to this domain helps to specify the intracellular location of the dynein more than twice the size of myosin II and four times more than the mass of conventional kinesin. Unlike myosin and kinesin, the predicted secondary structure of the dynein sequence does not readily divide into a globular head and a tail domain.

INVOLVEMENT OF DYNEIN IN ALZHEIMER

Axonal transport is essential for the movement of vital proteins, vesicles, organelles, signaling molecules, and other materials to the axon, and between the cell body and synapse. In neurodegenerative diseases such as Huntington's Disease (HD), Alzheimer's Disease the role of axonal transport defect was established by substantial evidence. The role of APP in axonal transport may be carried out by directly interacting with kinesin light chain in a binary complex, or indirectly in a ternary complex with a Jun-kinase scaffold protein called JIP1, which may be required for transport of APP vesicles themselves. [44,45]

Recent evidence has linked mutations in the cytoplasmic dynein 1 pathway to transport defects and motor neuron degeneration conditions, such as amyotrophic lateral sclerosis (ALS). Homozygous dynein HC null mutant mice were previously reported to exhibit preimplantation embryonic lethality; no phenotype was observed in heterozygotes. These results are consistent with a role for dynein in basic cellular functions, such as mitosis, but a role in neuronal transport and viability was not evaluated. Mutations in dynein itself have also now been implicated in motor neuron degeneration.[46]. Two mutations within the N

terminal part of the dynein HC were identified in chemically induced mutant mouse strains that exhibited neurological deficits.

Cytoplasmic dynein is the major motor of retrograde axonal transport.[47] As such, the impairment of its function appears able to lead to axonal transport dysfunction. Cytoplasmic dynein is also the molecular motor responsible for transport of misfolded proteins for their degradation and is thus crucially involved in the appearance and clearance of protein aggregates. Last, dynein is the molecular motor responsible for retrograde signaling from the synapse to the cell body. This mechanism is involved in cell to cell communication in the nervous system and its dysfunction might account for the noncell autonomy of neuronal death in NDDs. Cytoplasmic dynein is thus at a nexus of various pathophysiological mechanisms in NDDs. Here, we will first review the structure of the molecular motor and the potential consequences of its dysfunction. We will then critically review the evidence that involves directly or indirectly dynein in neurodegenerative diseases, such as motor neuron diseases (including ALS), basal ganglia degeneration (mostly HD and PD) and dementia (including AD).

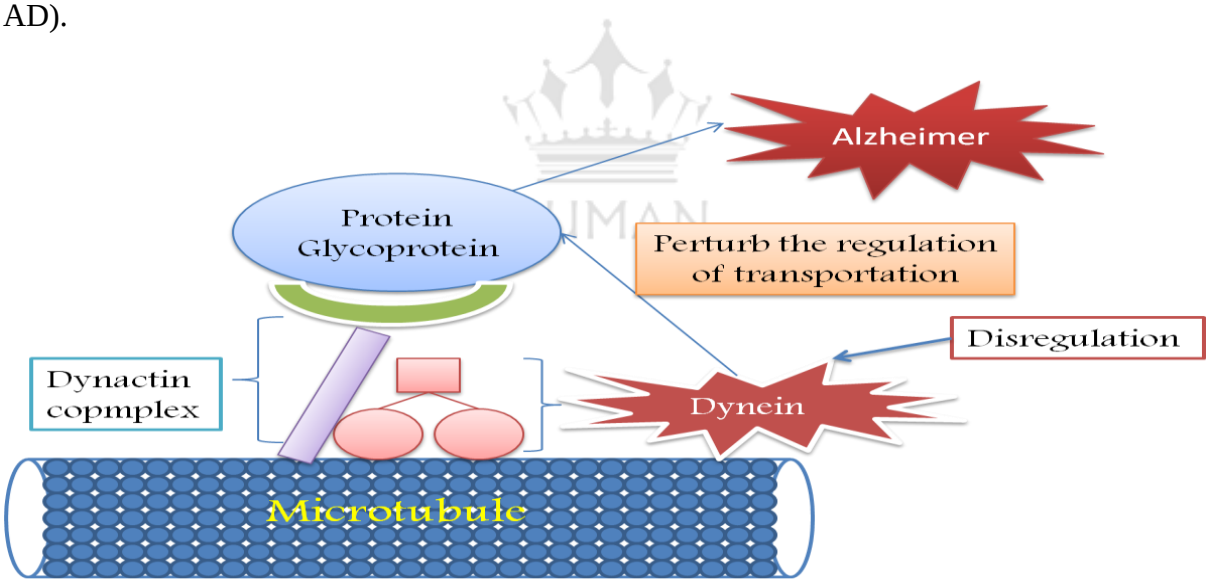

Fig. 2 Dysfunction of dynein leads to neuronal death

Evidence involving dynein in the AD is largely indirect and dynein might be involved in both amyloid plaques and neurofibrillary tangle neurotoxicity. Indeed, as would be expected if the AD is associated with decreased dynein function, the AD is associated with a number of axonal defects and swellings, and these defects are present in human AD brains, but also in animal models long before cognitive deficits are obvious.[43,48]However, observations of axonal defects and swellings should not be taken as proofs of axonal transport defects or of

dynein involvement. In the case of an AD, such evidence is still lacking. The APP, the precursor of Aβ peptide, is transported by fast axonal anterograde transport, is the subject to complex trafficking events[49] and accumulates in pathologically enlarged endosomes. [50,51] A number of evidence suggest that Aβ is transported to the synapse where it is secreted [52] and a number of laboratories have focused their efforts in determining whether the amyloid cascade might be related with axonal transport impairment. APP has been found to be interacting with kinesin-1 [53], but this has since been refuted[69] More recently, Aβ peptide was shown to disrupt axonal transport in cultured neurons.[54,55]. Whatever the underlying mechanism, most evidence linking axonal transport machinery to amyloid plaques suggest an involvement of rather anterograde transport than retrograde transport. For instance, the reduction in kinesin gene dosage enhanced axonal pathology in AD animal models [56], while no similar evidence has been published concerning dynein. The function of the APP itself in axonal transport is also unclear since APP deletions did not modify axonal transport, while APP overexpression leads to axonopathy in an Aβ-independent manner [57]. The links between APP and axonal transport in general, and dynein in particular, thus remain largely unclear.

Recent studies showed that APP accumulates in enlarged endosomes during normal aging and AD. Endosomal pathology in the AD is a very early event that precedes Aβ deposition [58]. Interestingly, increasing endocytosis through Rab5 overexpression largely mimics AD-related endosomal pathology, increases Aβ deposition and promotes neuronal apoptosis [59]. Dynein function is required for the Rab5-mediated increase in endocytosis [60], suggesting that dynein function might increase Aβ deposition through the facilitation of Rab5 mediated endocytosis. However, knocking down dynein in neurons mimicked aging-induced endosomal pathology, led to the accumulation of APP in endosomes and increased beta-secretase cleavage of APP, leading to increased production of Aβ [61]. Thus, dynein might be required for Aβ production, but its loss might also interfere with endosomal trafficking of APP and accelerate amyloid plaque deposition. Further work is needed to resolve this discrepancy. The second typical lesions of the AD are neurofibrillary tangles (NFT), mainly composed of accumulations of hyperphosphorylated tau. Interestingly, Tau is a microtubule-associated protein, that was recently shown to differentially regulate kinesin and dynein motor activity [62]. Tau is also a binding partner for dynactin and enhances dynactin binding to microtubules [63]. Last, very recently, Tau reduction was shown to prevent Aβ induced defect in axonal transport, both in anterograde and retrograde directions [64]. Thus, this

crucial player in AD pathogenesis appears also a potential modulator of dynein-dependent transports.

Worthy of note, that recent data demonstrate a novel pharmacological link between dynein and AD. Therefore, we have compiled the whole structural mechanistic approach & pathological role of dynein in the AD. This compilation of data will provide a new path of research beyond the boundaries. Those scientists working on the treatment of AD finds a new gate opening to eradicate this disease.

CONCLUSION

The Alzheimer is a neurodegenerative disorder rapidly growing and threatening in the modern world. The causes and symptoms are known but effective treatment is not available recently. Scientists study and focus the molecular mechanism of Alzheimer and try to solve the mystery related to this disease. In the molecular mechanism, the dynein also takes part in the formation of disease. Hence here we compile the data of dynein and Alzheimer. In the future focus of this protein is effective for treatment in various diseases.

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