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Studying Alzheimer's Disease Using *Drosophila melanogaster* as a Powerful Tool

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Abstract

Background: Alzheimer's disease (AD) is an increasingly prevalent neurodegenerative disease characterized by protein aggregation in the form of amyloid plaques containing beta-amyloid peptides and neurofibrillary tangles containing hyperphosphorylated tau protein. The central molecular events underlying AD pathogenesis remain controversial and poorly defined. *Drosophila melanogaster* has emerged as an important genetic resource for studying the pathology of AD. Many AD models have been created using *Drosophila*, taking advantage of its short generation times, sophisticated genetic tools, and abundance of homologs to human genes. **Purpose:** This review summarizes different models for studying AD in *Drosophila melanogaster,* including the full-length APP, C99, Aβ42 and Tau models, explaining how the models were built and what we have learned from them. **Conclusion:** Four main AD *Drosophila* models are introduced in this review, which can serve as a future method to investigate genes and drugs that can modify symptoms.

Keywords

Drosophila, Alzheimer's Disease, APP, C99, Aβ42, Tau

1. Introduction

Alzheimer's Disease (AD) is the most common type of dementia that affects over 6 million people in the United States [1]. In the 2020 US Census, the prevalence of AD jumped from 5.3% in people 65 to 74 years old to 34.6% in people aged 85 and older [2]. Globally, the number is projected to rise from 57.4 million in 2019 to 152.8 million in 2050 [3].

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The first symptom of AD is a gradual memory decline. In later stages, as memory degenerates, language skills and basic body functions such as swallowing and bladder control also deteriorate [4]. At the neuropathological level, there are two main hallmarks of AD which were noted by Dr. Alois Alzheimer upon his discovery of AD back in 1906: amyloid plaques and neurofibrillary tangles [5].

Amyloid plaques are chiefly composed of amyloid-beta peptides (Aβ), created from the cleavage of a transmembrane protein called the amyloid precursor protein (APP). APP is cleaved by β-secretase, which yields sAPPβ and C99. The C99 domain is then cleaved by γ-secretase, breaking off into an intracellular fragment, AICD, and different forms of Aβ due to imprecise cleavage by γ-secretase (**Figure 1**). One of these forms is called Aβ42, which is considered significantly toxic. Aβ42 gives rise to Aβ amyloid fibril formation. These Aβ amyloid fibrils later form amyloid plaques, eventually leading to cell death [6]. The theory that this accumulation of Aβ is the chief cause of AD is called the amyloid hypothesis, first introduced by Dr. John Hardy and Dr. David Allsop in 1991 [7]. This has been the main hypothesis driving AD research and drug development for decades.

Neurofibrillary tangles are made up of hyperphosphorylated tau proteins. In the healthy brain, tau proteins play a critical role in stabilizing microtubules (MTs), which support the growth of neurons [8]. In AD patients, however, the phosphorylation of tau leads to its detachment from MT. These tau proteins then stick to each other, creating neurofibrillary tangles around neurons. The number of neurofibrillary tangles correlates with the severity of the clinical symptoms of

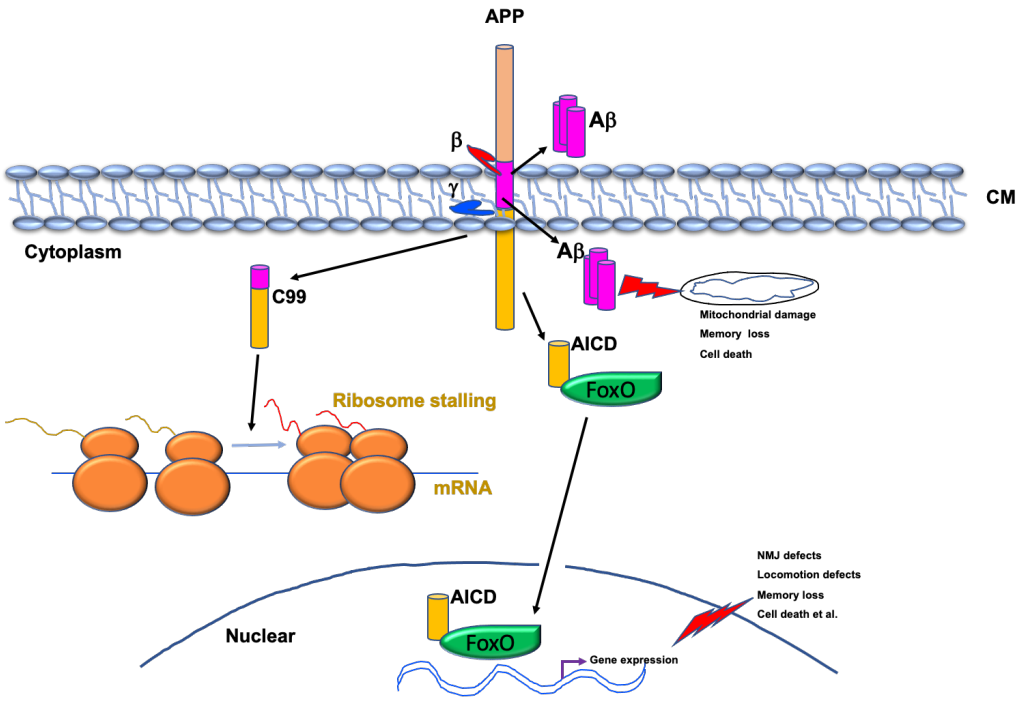

Figure 1. The procession of APP and its function.

AD [4]. The theory that hyperphosphorylated tau proteins are the leading cause of AD is called the tau hypothesis.

AD has been studied in many different model organisms, most notably the mouse [9] [10] and *Drosophila melanogaster*. This review summarizes the different models for studying AD in *Drosophila melanogaster*, explaining the models and what was found employing them.

2. Why Use *Drosophila*?

Drosophila melanogaster has been used for over 120 years and has emerged within the past five decades as a preeminent model for genetics research [11]. There are many benefits to using this complex organism, the most noteworthy of which is its homology to humans at the gene and genomic levels. We share around 75% of our genes with *Drosophila* [12] [13]. Importantly, when homologs of human disease genes are introduced into *Drosophila*, they can cause a range of disease phenotypes, including cancers and neurodegenerative diseases such as AD [14]. *Drosophila* can also be a great research tool because of its complexity, as behaviors such as memory and learning can be studied [15]. Another thing that sets *Drosophila* apart from other organisms used to study genetics is that it is easy to be manipulated in genetics. In addition to being a robust genetic tool, *Drosophila* is easy to be used because of its short life cycle. *Drosophila* is an organism that has a four-stage life cycle: egg, larva, pupa, and adult. Egg production by a female fly can reach up to approximately 100 eggs per day [16], and it only takes ten days at 25˚C for *Drosophila* to mature from an embryo to adulthood [11]. On average, *Drosophila* has a life span of 2 - 3 months [17], making it easier to be used to study age-related diseases such as AD.

Specific to neurodegeneration, *Drosophila* is an effective tool because it responds strongly to factors such as Aβ42 and tau protein implicated in AD. Neurons die from overexpression of these disease-associated factors, and this neuronal loss manifests as distinctive phenotypes such as reduced locomotion, rough eye texture, or abnormal wing posture [18] [19] [20], which are easy to be scored by the naked eye or under dissecting microscope. For these reasons, *Drosophila* is an optimal model for studying genetics, specifically neurodegenerative diseases such as AD.

3. *Drosophila* AD Models

3.1. Full-Length APP Model

The amyloid precursor protein (APP), or in *Drosophila* the amyloid precursor-like protein (APPL), is a single-pass transmembrane protein with a large extracellular domain [21]. The normal physiological function of APP is still not well understood, but it has been shown to regulate synaptic structure [22] and neurogenesis [23] [24]. Animal model studies have supported its role in the development of AD [25] [26].

In *Drosophila*, one way to study APP pathobiology is to overexpress it in the

nervous system. Pirooznia *et al.* used a *Drosophila* AD model to study the effect Tip60 HAT on APP, targeting the developing central nervous system [27]. Tip60 (Tat-interactive protein-60 KDa) is a member of the MYST family of Histone Acetyltransferases (HATs) [28]. Tip60 plays a role in DNA repair and apoptosis [29] and has been linked to the development of AD [30]. In a fly model that overexpressed human APP full length or human APP without the C-terminal domain (APP-deltaCT), the authors expressed wild type Tip60 or HAT-defective dominant negative Tip60 and found that Tip60 loss heightened the lethality effect of APP, whereas wild type Tip60 overexpression suppressed these lethal effects. It was also found that Tip60 and APP interacted with each other to mediate nervous system-specific development, a process that was dependent on Tip60 interaction with the C-terminal domain of APP. As mentioned above, Tip60 plays a role in apoptosis. Interestingly, coexpression of Tip60 suppressed neuronal apoptosis induced by APP. Collectively, these findings suggest that Tip60 and APP interact with each other to play a role in neuronal development and neuronal apoptosis in *Drosophila*.

Another study that employed the nervous system to study APP in *Drosophila* was reported by Wang *et al.* [31]. They investigated FoxO (forkhead box O), a protein that helps maintain cellular quality control and modulate homeostatic processes including apoptosis [32] [33]. Wang *et al.* first established that APP could induce cell death in *Drosophila* not only in the nervous system but also in developing non-neural tissues. They also showed that cell death from APP was dependent on APP intracellular domain (AICD) and that dFoxo was required for such APP-induced behavior. They concluded that through the release of AICD, APP induced FoxO-mediated cell death. Consistently, Wang *et al.* looked at the effect of AICD on the transcription of FoxO target genes and found that AICD served as a transcriptional cofactor of FoxO to activate the expression of Bim, a gene involved in apoptosis [34] (**Figure 1**).

For studying the function of APP in *Drosophila*, the wing is also a helpful model. Peng *et al.* studied Polo kinases and their effect on APP-induced phenotypes [35]. Polo kinases are involved in cell division and cell cycle progression [36] [37], and specific Polo-like kinases (Plk1 and Plk2) have been shown to play a role in the pathology of AD [38] [39]. Through a genetic modifier screen, the authors found Polo as a line that suppressed the wing phenotype induced by APP. They further investigated Polo/APP relationship by studying the neuromuscular junction (NMJ) and found that the depletion of Polo suppressed an increase of boutons and branches at the NMJ caused by overexpressing APP, and that Polo ameliorated larval locomotion defects induced by APP expression at the NMJ. Next, the authors tested a series of behavioral defects induced by APP: locomotion decline, shortened lifespan, and male courtship choice dysfunction (used as a model for cognitive ability). They repeatedly found that a loss of Polo ameliorated these deficits. They lastly targeted the eye, where APP induces a rough eye phenotype, and found that a knockdown of Polo partly suppressed the APP-induced retina neurodegeneration. Together, these data demonstrate that

Polo is required for APP induced NMJ and locomotion defects.

3.2. C99 Model

APP.C99 is an important APP fragment for studying AD pathology, as there is much evidence demonstrating that C99 accumulation is involved in AD. Different AD models from mice [40] [41] [42] to monkeys [43] have shown heightened C99 accumulation. C99 can also cause AD in an Aβ-independent manner in mammalian models [44] [45]. There is a paucity of studies on AD pathogenesis by the C99 fragment using *Drosophila* as a model. In a recent study [46], Rimal *et al.* used *Drosophila* to express APP.C99 driven by *Mhc*-Gal4 in the muscle, which resulted in a droopy wing or a held-up wing posture. These postures indicated muscle degeneration. A series of tests of *Drosophila* expressing C99 in the muscle and in postmitotic neurons showed that C99 increased mitochondrial fragmentation, reduced locomotor activity, led to synapse loss, and impaired aversive taste memory. These data showed that the fly C99 model displays many of the same features as AD. Rimal *et al.* next overexpressed and knocked down different genes, identifying what rescued or worsened the abnormal wing posture. They found that the ABCE1 protein, a ribosome recycling factor, rescued translational stalling of C99 and the abnormal wing posture when overexpressed. These results supported the notion that ABCE1 is involved in the stalled translation of C99. Rimal *et al.* next tested ZNF598, a sensor of ribosome stalling and collisions, to test the effect of ribosome-mediated quality control on C99 translation. ZNF598 RNAi reduced C99 stalling and rescued the abnormal wing posture that was a consequence of C99 toxicity. Moreover, ZNF598 rescued endosomal and lysosomal deficits in the muscle tissues of flies expressing C99. Lastly, Rimal *et al.* tested how different proteins impacted the CAT-tailing of C99, a ribosome collision/stalling product. This is important because CAT-tailed C99 leads to degeneration of the neuronal cell body, which was also observed by Udagawa *et al.* [47]. They found that ZNF598 RNAi, overexpression of ABCE1, and RQC factors decreased the number of CAT-tailed species. Collectively, the study by Rimal *et al.* showed that stalled translation of C99 and resultant CAT-tailed C99 led to proteostasis failure, leading to the development of amyloid plaques and neuronal death.

3.3. Aβ42 Model

Aβ40 and Aβ42 have been known to be the primary components of the senile plaques of the AD brain for decades [48]. Cellular studies have shown that Aβ42 may be more toxic than Aβ40. Whether an accumulation of amyloid plaques is the root cause of AD has been debated since the hypothesis was first formed [49]. Up to now, even with the recent approval of Aducanumab [50], a drug that targets amyloid-beta plaques, a consensus has not been made. In *Drosophila*, pan-neuronal expression of Aβ42 can lead to locomotor deficits, neurodegeneration of brain regions, and premature death in aged animals [51]. Various studies

have used *Drosophila* as a model to investigate Aβ42 in AD. Some of the most prevalent tissues used as targets to study Aβ42 in AD are the eye and the nervous system.

The eye is a popular region to target for neurodegenerative diseases as it is complex and accessible [52] [53]. A common theme is that the more Aβ42 is expressed, and the older the fly, the more severe the eye phenotype becomes. Using the *Drosophila* eye, Hua *et al.* studied the impact of zinc and copper on Aβ42 expression [54]. They tested this by raising or keeping flies in zinc or copper-enriched food and measuring the survival rates of flies expressing Aβ42 with copper and zinc supplements as well as a copper and zinc chelator, DP-109, and found that survival rates of Aβ42 expressing flies were decreased further with zinc but not copper and that DP-109 increased the number of Aβ42 expressing flies reaching adulthood. They also tested locomotion using a climbing assay, which worsened with age in Aβ42 expressing flies, and found that zinc further deteriorated locomotion. Another critical finding was with overexpression or removal of a regulator of metal homeostasis called MFT-1 (Metal Responsive Transcription Factor), where they found that overexpression of MFT-1 alleviated Aβ42 toxicity, whereas removal of MFT-1 (in a null mutant background) led to the eye phenotype getting significantly more severe.

Another study that utilized the *Drosophila* eye to study Aβ42 is by Sarkar *et al.* on the effects of the protein Lunasin to reverse the toxicity of Aβ42 [55]. Lunasin is a soy protein with an antioxidant and anti-cancer effect [56] [57] [58]. They used *GMR*-Gal4, which drives gene expression in the eye, and found that the neurodegenerative phenotype of *GMR* > Aβ42, which includes axon targeting defects in the eye, was significantly rescued by the misexpression of Lunasin (*GMR* > Aβ42 + Lun).

Another important target tissue for AD study is the mushroom body, which is part of the central brain regions of *Drosophila*. The mushroom body is associated with a multitude of complex behaviors such as taste memory and learning as well as locomotor activity [59] [60], and therefore it is widely used to study neurodegenerative diseases [61]. Iijima-Ando *et al.* used the mushroom body structures of *Drosophila* to express Aβ42 to study the effects of Neprilysin (NEP), an amyloid-degrading enzyme that can slow the progression of AD [62] [63] [64]. Iijima-Ando *et al.* expressed Aβ42 in the ER of the mushroom body of *Drosophila* and then coexpressed NEP proteins in these Aβ42 fly brains. From this, they found that NEP significantly reduced the level of Aβ42 in the Aβ42 expressing flies. They also found that NEP suppressed the neuronal loss induced by Aβ42 expression. However, they found that overexpression of NEP did not rescue the Aβ42 induced premature fly death. In fact, the expression of NEP shortened the lifespan of *Drosophila* relative to the control. Overexpression of NEP also caused axon degeneration and decreased CREB-mediated transcription in the fly.

Iijima-Ando performed another interesting study employing mushroom body structures to test the brains of Aβ42 flies [65]. In this study, Ijimia-Ando *et al.*

expressed mito-GFP and Aβ42 in the mushroom body structure and found that the number of mitochondria is reduced in the axons and dendrites of the Aβ-42 fly brain but not in the cell body, showing that expressing Aβ42 does not result in a global decline in mitochondria but rather in mitochondrial mislocalization. A lack of mitochondria in the axons has been shown to disrupt the cAMP/PKA signaling, which reduced synaptic strength. They found that decreasing the cAMP levels led to Aβ42 induced locomotor defects occurring earlier. Additionally, neuronal knockdown of PKA intensified the locomotor defects induced by Aβ42. From these results, they concluded that neuronal dysfunctions in Aβ42 flies could be a product of cAMP/PKA signaling reduction along axons and dendrites.

A more recent study used the mushroom body of Aβ42 expressing *Drosophila* to investigate the involvement of mitochondrial dysfunction [66]. Just like Iijima-Ando, the authors expressed Aβ42 and mito-GFP to look at the effect of Aβ42 on mitochondria in the neurons of *Drosophila*. They found that Aβ42 causes fragmentation of somatic mitochondria in flies starting on their first day of life. They then investigated whether the mitochondrial fragmentation observed was neuron-wide or specific to the soma of the mushroom body neurons and found that mitochondrial fragmentation first occurred in the soma, then in the dendrites, and lastly in the distal axons. The authors next studied the effect Aβ42 had on mitochondria, measuring the calcium import of the mushroom body neurons. They found that by day 5, mitochondrial calcium import decreased significantly in Aβ42 expressing flies, indicating an impairment of the somatic mitochondria in the mushroom body neurons. They also looked at how Aβ42 impacted apoptosis since mitochondria play a critical role in programmed cell death [67], and found that as time passed, there was a heightened level of apoptosis in the soma of the Aβ42 *Drosophila*. Lastly, they investigated the effect of expressing Aβ42 in the mushroom body neurons on memory and found that after 15 days, a significant memory impairment was observed. This study establishes the *Drosophila* model as a useful in *vivo* system for probing the mechanisms by which Aβ42 produces mitochondrial toxicity that contributes to memory dysfunction.

3.4. Tau Model

Tau is a microtubule-associated protein, typically found in the axons, that works to maintain the stability of microtubules [68]. In AD, tau becomes hyperphosphorylated 3 to 4 times more than in a normal adult brain [69] [70] and disrupts microtubule integrity [71] [72]. The free tau molecules then aggregate into helical patterns [73]. In *Drosophila*, expressing human tau has been shown to impair olfactory and motor learning and disrupt the mushroom body neurons [74] [75].

One of the most common models to study tau in *Drosophila* is the eye. Nishimura *et al.* studied the effects that PAR-1 kinase had on tau toxicity in a *Drosophila* AD model [76]. In this study, they looked at the interactions between

PAR-1 and tau and found that photoreceptor degeneration caused by tau was partially suppressed by the removal of PAR-1. In addition, they found that overexpression of PAR-1 enhanced the toxicity of a mutant form of human tau (h-tau) associated with frontotemporal dementia. They used the 12E8 antibody, which recognizes p-S262 and p-S256 sites of h-tau, and they found that overexpression of PAR-1 can lead to increased phosphorylation of human and fly tau at the residues detected by 12E8. They also found that the phosphorylation by PAR-1 at the S262 and S256 sites are prerequisites for the phosphorylation by kinases such as GSK-3 and CDK5 at other sites. Their data suggested that PAR-1 phosphorylation at the 12E8 sites provides docking sites for kinases such as GSK-3 and CDK5 to prime the phosphorylation of other nearby sites.

Another group that used the eye to study tau in the *Drosophila* AD model was Zhang *et al.* [77]. This study specifically examined the effect of Salidroside (Sal) on a *Drosophila* tau model. Sal is a glycoside with a strong antioxidative, anti-inflammatory, and anti-apoptosis effects [78] [79]. Zhang *et al.* expressed tau in the CNS and the eyes and examined the effects of Sal. They fed Sal or Donepezil (a clinically approved drug for AD) to tau transgenic *Drosophila* in different concentrations and tested for survival rate. They found that Sal treatment increased both survival rate and time comparably to Donepezil. They also found that Sal treatment improved the climbing ability of tau transgenic flies after 30 days. Vacuoles in the brain are hallmarks of *Drosophila* neurodegeneration, so they also fed tau transgenic flies with Sal and observed vacuoles. They found that the Sal treatment prevented the histological abnormalities in the vacuoles. Lastly, Zhang *et al.* investigated the pathways affected by Sal and found that Sal increased the level of p-GSK-3β, which is part of a pathway that prompts neuronal survival and plays a role in the pathogenesis of AD [80] [81], while decreasing levels of p-tau that is a downstream target of GSK-3β.

Anupama *et al.* also studied a tau induced AD model of *Drosophila* [82]. They examined the effect of Jatamansinol on the neurotoxicity induced by tau. N. jatamansi is an herb whose root extract can decrease Aβ42 toxicity in *Drosophila* [83]. They gave tau expressing flies different doses of jatamansinol-supplemented food and found that compared to the control flies fed with normal food, flies fed with Jatamansinol supplements showed increased survival rates and improved locomotor activity. They also found that tau expressing flies fed with jatamansinol supplements showed a significant decrease in the amount of tau protein compared to the control in all age groups. They then tested for learning and memory and found that flies fed with jatamansinol food had a significantly higher memory performance index than the control. Next, Anupama *et al.* examined tau induced eye degeneration and found that there was a significant reduction in the amount of eye degeneration in flies fed with jatamansinol-supplemented food. Next, they tested jatamansinol treatment of the control flies and found that compared to the regular food group, there was a reduction of reactive oxygen species, suggesting that jatamansinol improves antioxidant de-

fense. Lastly, they found that jatamansinol also inhibits the cholinesterase enzymes, which are disturbed in AD [84].

4. Conclusion

Drosophila melanogaster is an excellent tool for studying the pathology of AD, as it shares 75% of our genes. In addition, neurodegeneration in *Drosophila* manifests in obvious phenotypic changes. Furthermore, *Drosophila* is a great model system because of its short generation times and facile genetic analysis. Given that *Drosophila* is such an effective tool for studying AD, in this paper, we examine some of the models for studying this disease, going over how they were performed and what was found. The first model examined is APP Full Length, focusing on the two popular targets: the nervous system and the wing. Next is the C99 model, which has been employed recently to reveal the importance of ribosome-associated protein quality control in AD pathogenesis. Then the Aβ42 *Drosophila* models of the eye and the mushroom body are discussed, which are popular for studying AD since the eye is complex and accessible, and the mushroom body can be used to study learning and memory. Last, the tau protein *Drosophila* model is discussed, focusing on the eye, which is a common target. It is anticipated that the continued use of these models will deepen our understanding of AD pathogenesis and uncover novel drug targets for combating AD.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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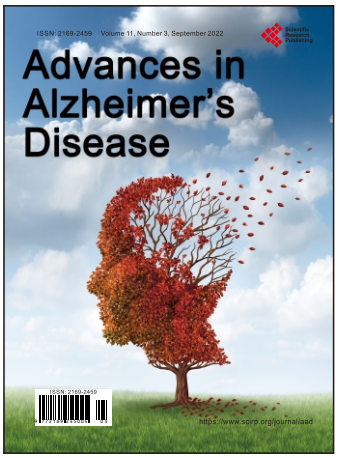

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