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Drosophila a Newtechnology to Test Therapeutics of Alzheimer'sdisease

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ABSTRACT
In an effort to pinpoint the molecular pathways linking clinical indicators such aggregating Tau and Aβ peptides to neurodegeneration and eventually to the progressive memory loss seen in AD, a variety of model systems have been developed recently. However, crucial elements of the disease's aetiology are still unknown, and there is currently no cure. Drosophila genetic research has been conducted for more than a century. It serves as the main model organism for experimental studies of multicellular eukaryotic biology because it combines genetic, anatomical, behavioural, methodological, and even pecuniary advantages. Therefore, this review is carried out while taking these facts into account. The potential drosophila model that is currently accessible will be thoroughly examined and discussed in this paper using various databases. To work around this issue, researchers have developed direct secretion of human Aβ42 or triple transgenic flies expressing human APP, β-secretase, and Drosophila γ-secretase presenilin (dPsn). It aids in the molecular and cellular understanding of therapeutic actions.

Keywords: Alzheimer, Drosophila, neuroprotective, mechanism, molecular, therapeutic

I. INTRODUCTION

The increased life expectancy of the general population and a greater understanding of the socioeconomic effects of the disease have made Alzheimer's disease (AD) a serious public health issue. Progressive memory loss, disorientation, and pathological markers (senile plaques and neurofibrillary tangles) were used by Alois Alzheimer to characterise it in 1906.At first, AD was thought to be a rare condition, and later, it was thought to be an unavoidable side effect of ageing. Ageing stigma and other factors prevented early diagnosis and treatment of AD patients, but these misunderstandings are dissipating, and therapieseven if they were at first ineffectiveare now becoming available [1].

In order to diagnose Alzheimer disease (AD), neurofibrillary tangles and plaques containing the protein tau must be present. An amnestic cognitive impairment characterises AD's prototypical appearance, while non-amnestic cognitive impairment characterises its less common variations. AD is a hereditary and sporadic neurodegenerative disease. Although other neurodegenerative and cerebrovascular disorders might affect AD's clinical effects, AD is a common cause of cognitive impairment that develops in midlife and later in life. The brain disorder caused by the loss of synaptic homeostasis and dysfunction in the intricately linked endosomal and lysosomal clearance pathways, in which precursors, aggregated species, and post-translationally modified forms of Aβ and tau play significant roles, is how this primer conceptualises AD biology. Therapeutic efforts are still having trouble identifying targets in available models [2].

A number of model systems have been created in recent years in an effort to identify the molecular pathways that connect clinical markers such aggregating Tau and Aβ peptides to neurodegeneration and ultimately to the progressive memory loss seen in AD. However, important aspects of the disease's aetiology continue to be elusive, and there is now no effective treatment available [3-6].

Specific functional facets of human diseases in general and neurodegenerative diseases in particular are studied using animal model systems. Yeast, Caenorhabditiselegans, animals, and human cell culture systems are all examples of AD models. No model system, however, combines ease of use with fundamental characteristics of AD, such as cognitive and behavioural impairment

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brought on by cell type-specific neurodegeneration, cellular pathophysiology, which includes aggregation formation, a distinct pattern of inheritance, and genetic homogeneity [3-6].

Genetic studies in Drosophila date back more than a century. It combines genetic, anatomical, behavioural, methodological, and even financial advantages and is utilised as the primary model organism for experimental research of multicellular eukaryotic biology. One of the first creatures to have its entire genome sequenced is this one. Only four chromosomes contain all of the approximately 13,600 protein-coding genes. The brain and neurological system of the fly have been extensively researched. Its anatomical characteristics, such as the compound eye, make phenotypic characterization simple. The behaviour of the fly varies from straightforward avoidance to learning and memory. There are many well-established molecular genetics tools accessible since the mouse has a long history of being used as an animal model in research. Another benefit is that it has a less life span[7-10].

So taking this facts in consideration, this review is conducted. In this review, we will comprehensively review and discuss the possible available drosophila model that can be used to explore therapeutic interventions of Alzheimer's disease.

II. METHODOLOGY

A number of widely used databases, including SciFinder, Google Scholar, MEDLINE, EMBASE, Scopus, PubMed, and Science Direct, were utilised to retrieve published papers (up until April 2023). We looked for and extracted published literature relating to Drosophila models to explore therapeutic interventions for Alzheimer's disease using the keywords "Drosophila", "neuroprotective", "nootropic", "Alzheimer","therapeutic", and "mechanism of action". The language of searches was limited to English.

III. DROSOPHILAMODELS

Fly models that focus on Tau or amyloid toxicity have been established to examine the underlying pathophysiology of Alzheimer's disease. Overexpression of human wild-type or mutant Tau results in axonal transport abnormalities, early mortality, and neurodegeneration that is reliant on ageing. Numerous kinases and phosphatases, apoptosis regulators, and cytoskeleton proteins have been discovered as determinants of Tau toxicity in vivo using large-scale screens using a neurodegenerative phenotype caused by eye-specific overexpression of human Tau. The vertebrate APP family members and the Drosophila APP ortholog (dAPPl) have the distinctive domains, however the human Aβ42 domain is absent. Researchers have devised methods through direct secretion of human Aβ42 or triple transgenic flies expressing human APP, β-secretase, and Drosophila γ-secretase presenilin (dPsn) to get around this problem [11].

3.a. APPmodel

Uncertainty surrounds the physiological function of the amyloid precursor protein (APP), a transmembrane protein with structural and functional conservation. The majority of APP biology research is concentrated on the part that contributes to familial Alzheimer's disease (fAD), which is caused by APP mutations. APP Like (APPL), a single APP homologue found in the fruit fly Drosophila melanogaster, was used in a study to examine the physiological role of APP in the adult brain. The role of APPL in neuronal wiring and axonal growth throughout development via the Wnt signalling pathway has been demonstrated in earlier research. However, just like APP, APPL continues to be expressed in all adult brain neurons, although it is unknown what its tasks are or what molecules and cells underlie them. Study shows reduction of APPL [12-13].

According to studies, APPL loss of function (LOF) causes dysregulation of endolysosomal function in neurons. This is accompanied by a considerable expansion of early endosomal compartments, neuronal cell death, and the accumulation of dead neurons in the brain during a crucial period at a young age. Reducing the amounts of the early endosomal regulator Rab5 can reverse these abnormalities, demonstrating that endosomal function contributes to cell death in a causative manner. The last set of findings demonstrate that in an axotomy model, the secreted extracellular domain of APPL interacts with glia and controls the size of their endosomes, the expression of the Draper engulfment receptor, and the removal of neuronal debris. A unique family of neuroglial signalling components necessary for adult brain homeostasis is represented by the APP proteins [14].

3.b. β-secretase model

The primary enzyme in the synthesis of β-amyloid (Aβ), which builds up in the senile plaques typical of Alzheimer's disease, is β-secretase (also known as BACE1). As a result, the absence of BACE1 limits the formation of Aβ and the β-processing of the amyloid precursor protein,

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making it a suitable target for therapeutic research. BACE1 has been linked to the cleavage of Neuregulin and a voltage-gated sodium channel subunit, but its loss is also harmful since it causes myelination abnormalities and altered neuronal activity. Glial survival depends on the Drosophila ortholog of BACE, dBACE. When dBACE is knocked down in photoreceptor neurons, the glia in their target zone, the lamina, gradually deteriorate, demonstrating that this is a non-cell autonomous function [15].

The dBACE homolog of BACE in Drosophila is necessary for glial survival. When dBACE is knocked down in photoreceptor neurons, the glia in their target zone, the lamina, gradually deteriorate, demonstrating that this is a non-cell autonomous function. It's interesting to note that while the degeneration is accelerated by an APPL variant that lacks secretion, this phenotype is inhibited by the absence of the fly's amyloid precursor protein (APPL). This demonstrates that full-length APPL in neurons encourages the death of nearby glial cells and that APPL processing is required to stop glial cell death. Therefore, these findings not only suggest that an APP protein has a unique function in glia, but also that this function is particularly controlled by β-cleavage [16].

3.c. γ-secretase presenilin model

The intramembrane aspartyl protease γ-secretase, which has been connected to a number of human disorders, including Alzheimer's disease, plays a crucial function in various signalling pathways involved in cellular differentiation. In this article, we present a transgenic Drosophila model for in vivo-reconstituted -secretase that relies on the production of epitope-tagged versions of the four essential -secretase subunits Presenilin, Nicastrin, Aph-1, and Pen-2. The effective assembly of mature, proteolytically active -secretase is promoted by the coexpression of these four elements, in keeping with earlier cell culture and yeast investigations. We show that the biochemical characteristics and subcellular localization of in vivo-reconstituted γ-secretase are similar to those of endogenous γ-secretase.

Studies show that the biochemical characteristics and subcellular localization of in vivo-reconstituted -secretase are similar to those of endogenous γ-secretase. But examination of the cleavage of substitute substrates in transgenic γ-fly assays uncovered unexpected functional variations in the activity of reconstituted γ-secretase towards various substrates, including noticeably diminished cleavage of some APP family members in comparison to cleavage of the Notch receptor. These results suggest that additional variables variably control the activity of γ-secretase towards its substrates in vivo under physiological circumstances. The study shows the general functionality of reconstituted γ-secretase in a multicellular organism and the necessity of substrate-specific variables for effective in vivo cleavage of particular substrates [17].

IV. CONCLUSION

Drosophila melanogaster is a practical in vivo tool for examining AD pathomechanisms. For instance, it is simple to identify Aβ42 aggregation in flies. As a result, the ability of numerous tiny molecules to suppress Aβ peptide aggregation can be tested. It is a simple, affordable tool to evaluate new medications, chemicals, and herbal treatments for Alzheimer's disease. It helps in understanding the therapeutic interventions at molecular and cellular levels.

REFERENCES

[1]. Schachter AS, Davis KL. Alzheimer's disease. Dialogues ClinNeurosci. 2000 Jun;2(2):91-100. Doi: 10.31887/DCNS.2000.2.2/asschachter. PMID: 22034442; PMCID: PMC3181599.

[2]. Knopman, D.S., Amieva, H., Petersen, R.C. et al. Alzheimer disease. Nat Rev Dis Primers 7, 33 (2021). https://doi.org/10.1038/s41572-021-00269-y.

[3]. Winderickx J, Delay C, de Vos A, Klinger H, Pellens K, Vanhelmont T, van Leuven F, Zabrocki P. Protein folding diseases and neurodegeneration: lessons learned from yeast. BiochimBiophysActa. 2008;1783:1381–1395. Doi: 10.1016/j.bbamcr.2008.01.020.

[4]. Teschendorf D, Link CD. What have worm models told us about the mechanisms of neuronal dysfunction in human neurodegenerative diseases? MolNeurodegener. 2009;4:38. Doi: 10.1186/1750-1326-4-38.

[5]. Gotz J, Chen F, Barmettler R, Nitsch RM. Tau filament formation in transgenic mice expressing P301L tau. J Biol Chem. 2001;276:529–534.

[6]. Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, Younkin S, Yang F, Cole G. Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice. Science. 1996;274:99–102. Doi: 10.1126/science.274.5284.99.

[7]. Adams MD, Celniker SE, Holt RA, Evans CA, Gocayne JD, Amanatides PG, Scherer SE, Li PW, Hoskins RA, Galle RF. Et al. The genome sequence of Drosophila melanogaster. Science. 2000;287:2185–2195. Doi: 10.1126/science.287.5461.2185.

[8]. Nichols CD. Drosophila melanogaster neurobiology, neuropharmacology, and how the fly can inform central nervous system drug discovery. PharmacolTher. 2006;112:677–700. Doi: 10.1016/j.pharmthera.2006.05.012.

[9]. McGuire SE, Deshazer M, Davis RL. Thirty years of olfactory learning and memory research in Drosophila melanogaster. ProgNeurobiol. 2005;76:328–347. Doi: 10.1016/j.pneurobio.2005.09.003.

[10]. Greenspan RJ. Fly Pushing: The Theory and Practice of Drosophila Genetics. New Jersey: Cold Spring Harbour Laboratory Press; 2004.

[11]. Prüßing, K., Voigt, A. & Schulz, J.B. Drosophila melanogaster as a model organism for Alzheimer's disease. Mol Neurodegeneration 8, 35 (2013). https://doi.org/10.1186/1750-1326-8-35)

[12]. Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature. 1991;349 (6311):704–706. Doi: 10.1038/349704a0.

[13]. Daigle I, Li C. Apl-1, a Caenorhabditiselegans gene encoding a protein related to the human β-amyloid protein precursor. Proc Natl AcadSci U S A. 1993;90 (24):12045–12049. Doi: 10.1073/pnas.90.24.12045.

[14]. Kessissoglou IA, Langui D, Hasan A, Maral M, Dutta SB, Hiesinger PR, et al. (2020) The Drosophila amyloid precursor protein homologue mediates neuronal survival and neuroglial interactions. PLoSBiol 18(12): e3000703. Doi:10.1371/journal.pbio.3000703)

[15]. Cai H, Wang Y, McCarthy D, Wen H, Borchelt DR, Price DL, Wong PC. BACE1 is the major beta-secretase for generation of Abeta peptides by neurons. Nat Neurosci. 2001;4:233–234)

[16]. Bonnie J. Bolkan, TilmanTriphan, and Doris Kretzschmar. B-Secretase Cleavage of the Fly Amyloid Precursor Protein Is Required for Glial Survival. J Neurosci. 2012 Nov 14; 32(46): 16181–16192. Doi: 10.1523/JNEUROSCI.0228-12.2012)

[17]. Stempfle et al. In Vivo Reconstitution of γ-Secretase in Drosophila Results in Substrate Specificity. Mol Cell Biol. 2010 Jul; 30(13): 3165–3175. Published online 2010 Apr 16. Doi: 10.1128/MCB.00030-10.