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Drosophila melanogaster as a Model to Study Human Neurodegenerative Diseases

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Abstract

The central nervous system (CNS) is the most complex part of the human body, which controls a variety of cellular and molecular activities. Neurobehavioral functions of CNS play a vital role in making appropriate responses to the environmental stimuli. Some kind of such responses can be maintained in neural networks due to neuronal plasticity. When brain ages, or being damaged by means of genetic or environmental factors, memories will disappear gradually. Molecular mechanism of memory formation and disruption are studied during normal and diseased conditions, respectively. However, it is far to understand the complete scenario and we need a model organism to undertake specific studies and unravel the mystery of neuronal function. The fruit fly, *Drosophila melanogaster* possesses many characteristics, which enable neuroscientists to model wide range of complex behaviors and find their neural circuit. Even though, many human neurodegenerative disorders (NDDs) can be modeled in this insect and provide unique opportunities for effective therapeutic interventions. Here I summarized few points on the contribution of *D. melanogaster* in the neurobiology of learning and memory as well as human NDDs.

Keywords: *Drosophila melanogaster*, Learning, Memory, Neurodegenerative Diseases

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Introduction

In the late 1800s and early 1900s, psychologists began to formalize the process of learning and memory in laboratory experiments. In this context, learning is defined as a durable modification in behavior due to a prior experience.[1,2] The perseverance of these behavioral responses over the time is known as memory. Memories can last for various lengths of time, which can be categorized into two main types short-lived and long-lived. Behavioral plasticity, which results in memory formation, is of one of the essential biological processes involved in fitness and survival of an organism. Study of behavioral plasticity is largely faced with the complexity of the neural circuits and behavioral responses.

Pavlov[3] formally distinguished two types of learning in the laboratory. One form was called non-associative learning, that could be either sensitization (an elevation in behavioral response due to encountering a single stimulus), or habituation (a decline in a behavioral response following exposure to a single stimulus). Another form of learning was called associative learning. That referred to a change in the behavioral responses due to a temporal association of two stimuli in time.[4] There are two basic types of associative learning. One is operant conditioning, which means that an animal is rewarded or reinforced for doing something in response to the stimulus. If the animal does not do the right response to the stimulus, it is not rewarded or it is punished. Another type of associative learning is classical conditioning or Pavlovian conditioning that includes a temporal association of 2 stimuli in time regardless of what the animal does in response to the stimuli.[5]

Several mammalian model systems have been employed to study the behavioral plasticity and age-related senescence in

neural function. In addition to a longer lifespan, their complex behavior machinery is not easy to measure, as it comprises engagement of highly entwined brain circuits. Therefore, a simple model organism is advantageous to study the mechanisms underlying memory formation and behavioral plasticity and neurodegeneration processes.

Drosophila melanogaster as a Model for Neurodegenerative Diseases

For more than ten decades since William Castle at Harvard University introduced *Drosophila melanogaster* as a model system, it has been used in laboratories for a wide variety of studies including genetics, cell biology, electrophysiology, and behavioral genetics. *D. melanogaster* is a harmless insect with small size, relatively short life cycle of 10-12 days at 25°C, which makes it possible to investigate a large number of animals sharing a similar genetic background. Therefore, behavioral phenotypes can be correlated with manipulations under test.

Drosophila melanogaster is a powerful model system for investigating the biology of neurodegeneration. *D. melanogaster* shares many functions with humans rendering this as a suitable model for studying human diseases. *D. melanogaster* is an extremely obedient genetic model for divulging the molecular basis of human diseases. In fact, there are numerous biological functions preserved between this fly and mammals. Something like 75% of human disease-causing genes have a functional homolog in *D. melanogaster.*[6] Fruit fly shows a variety of well-known behavioral responses like positive phototaxis, negative geotaxis, and courtship and mating. They are able to associate between certain cues of their habitat environment and establish a memory. On the other hand, rich repertoires of experimental methods have strengthened the experimental benefits of using *Drosophila* in order to dissect out the molecular players and cellular pathways involved in associative memory.

One of the very well established kinds of memory in *Drosophila* is olfactory conditioning associative memory. There is a number of reasons illustrating that olfactory memory is a subject for studying the neurological features of learning and formation of memories in general. There is a remarkable similarity between the structure and function of the olfactory neural system among different types of animals, especially insects and mammals. Thereby, the principles and findings established in studying a model organism can easily be extended to the others. On the other hand, some sensory neural systems (for example visual or somatosensory systems) show less similarity index between different species. Olfactory memory function could also be the subject of neurological studies, as many of model organisms own a keen olfactory system. Amazingly, *Drosophila* is enabled to comprehend a precise 3D picture of its environment through its compound eyes and skillful olfactory and learning functions. Moreover, olfactory memories are believed to be special in their own right. Odors can mediate immediate alteration in affective states and arousal level; produce a tremendously precise memory of associated emotional experiences, which can persist for decades. Classical olfactory conditioning is a well-established conditioning paradigm in *Drosophila,* which studies the capacity of flies to associate between olfactory stimulus and an aversive mechanosensory input. Quinn and Benzer[7] in 1974 were the first to demonstrate that flies can learn to avoid the odor, which was presented earlier in association with electric shocks. Later on, this model was improved by Tully and Quinn[8] by setting up critical training and testing parameters that have been extensively adopted by many researchers to date.

The GAL4/UAS System

A GAL4/UAS system is a genetic tool in flies that makes it possible to express transgenes in tissue-specific patterns. GAL4 is a transcription factor in yeast that can bind to upstream activating sequence (UAS) and activate the transcription process. The GAL4/UAS system in *Drosophila* works in the same manner as in the yeast. Two individual transgenic lines, one for control of expression and the other one for transcription of the selected gene, can be constructed, separately. This binary system offers a generation of two separate stock libraries, one library for GAL4 stocks and a separate library for UAS stocks. Direct cloning of the GAL4 gene under promoters and enhancers of specific tissues is another powerful approach called as enhancer detection used in the generation of *Drosophila* library with distinct GAL4 expression patterns[9]. Every GAL4 stock is referred to a driver and several drivers have been constructed by random insertion of the GAL4 containing transposable P-element in the *Drosophila* genome. Following insertion, the flanking regulatory elements, enhancers, and promoters induce the tissue-specific expression of GAL4 in each individual driver, which subsequently can bind to UAS and activate expression of the gene of choice in a spatially restricted manner. Therefore, by making a genetic cross between any of tissue-specific, GAL4 stocks and a UAS stock containing the selected gene; its tissue-specific expression will occur. Since GAL4 and UAS components are exogenous, there is no endogenous element for binding of GAL4. Therefore, the GAL4/UAS system will not induce non-specific expression of endogenous genes or the target gene in *Drosophila*. In addition, GAL4 over-expression seems to have no significant phenotypic effect in *Drosophila*. The main advantage of the GAL4/UAS system is the independence of expression control and activation of transcription.[9] By making use of GAL4/UAS, a number of *Drosophila* transgenic lines have been generated resembling human disorders.[10-12]

Neurodegenerative disorders (NDDs) are main conditions that lead to a remarkable mortality among elderly populations throughout the world. Although the majority of NDDs are sporadic, a ratio of 5%–10% have

been estimated to be hereditary.[13] In this connection, there are very well-known mutations in synuclein alpha (*SNCA)* gene to cause autosomal dominant Parkinsonism.[14] Likewise, mutations in microtubule associated protein tau (*MAPT*) gene can develop frontotemporal dementia with pakinsonism (FTDP) via formation of neuronal Tau tangles.[15] To combat the pathogenic events occurring in neurons, we need to unravel the mechanism of action of genetic factors that play key roles in these diseases.

Many human NDD can be studied using the fruit fly, *D. melanogaster*. This is because large numbers of disease-causing genes share a homolog in *D. melanogaster* genome.[16] However, there are some disorders that their counterpart genes have not been identified in any incest. By the help of Gal4/UAS genetic tool, we have demonstrated that overexpression of human genes of interest in *Drosophila* neurons exerted neurotoxicity providing an opportunity to scrutinize genes involved in these pathways and to address few therapeutic interventions.

Overexpression of mutated human alpha-synuclein in *Drosophila* exhibits symptoms that are found in PD patients including locomotion defects.[14,17] The transgenic *Drosophila* models expressing MAPT have shown premature death accompanied by cognitive dysfunction.[18] We also created the first transgenic fly model of a NDD by expressing ε3 and ε4 isoforms of human apolipoprotein E (ApoE).[19] ApoE4 is the strongest known genetic risk factor for Alzheimer's disease development so far. The constructed genetic model exhibited progressive neurodegeneration, shortened lifespan, and memory dysfunction. Considering the mystery underlies APOE-mediated neurodegeneration, *Drosophila* model may facilitate analysis of the molecular and cellular events implicated in human *ApoE4* neurotoxicity.

Drosophila Model to Environmental Toxin-Induced Neurodegenerations

Besides genetic factors, many environmental stimuli are able to develop neurodegenerative conditions in human beings. Most of these factors include toxic and chemical agents such as insecticides, herbicides, and ethanol and so on. Almost all these agents promote an excess generation of free radicals, imbalance oxidative status of cells imposing sensitive tissues an oxidative stress (OS) condition. OS is involved in a wide range of disorders including NDDs.[13] Although there are well-characterized mechanisms explain OS-mediated cell damages, the complete scenario remains to be elucidated.[20] The fruit fly can be a suitable in vivo model organism for this type of researches. We could model parkinsonism in flies through chemical neurotoxins like paraquat and ethanol and show in part, how they can induce neurodegeneration[21]. Moreover, both the genetic and environmental factors can be possibly combined in *Drosophila* to investigate possible gene-environment interactions that might be involved in neuronal disease condition.[22,23]

Current Facilities and Future Perspectives

Advanced fly research laboratories are set up in Iran in very recent years. Department of Biology, University of Zabol and Genetic Research Center of University of Social Welfare and Rehabilitation Sciences have initiated research activities focused on familial intellectual disability (ID). ID is considered as a multi-factorial disorder with a high prevalence that imposes remarkable social and cost burdens on society. During an extensive case-control study in Iran, a number of novel genetic mutations have been identified which are associated with the disorder. Although these genetic factors can be undertaken as diagnostic markers, their functional role needs to be vetted to propose better-aimed therapeutic interventions.

In this connection, a small fly lab has been established in the center. The specific aims of this action are to evaluate functional role of novel genetic variations associated with human intellectual disability in an in vivo model system, to introduce the mechanism of actions through which these mutations deregulate human brain function and result in intellectual disability, and propose a novel genetic interaction network involved in human ID. The final goal is assisting in the establishment of more efficient medical considerations for ID treatment.

These kind of studies can be expanded and target more features of molecular defects underlying ID. This objective can be achieved by including more genes and other elaborated neurobehavioral analyses. Once relevant genes that lead to the disorder are identified and fly models are generated, drug screens can be performed in the future to identify drugs that will ultimately help the patients.

Conclusion

Taken all together, it is to be concluded that fruit fly, a tiny model organism, can be used to explore molecular mechanisms behind many genetic variations leading to human genetic disorders. This is not restricted to NDDs, rather could cover a wide spectrum of diseases such as retinal degeneration, muscular dystrophies, cardiovascular malfunctions, metabolic disorders and so on. There is a huge number of published studies on fly models of human diseases in the past 30 years, which serves a major contribution to the medical society for developing diagnostic and therapeutic inventions. Now, it is crucial to establish more fly labs in our medical research centers.

Ethical Approval

Not applicable.

Competing Interests

The author declares no conflict of interest.

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