

***Drosophila melanogaster*: Key Model Organism for the Study of Alzheimer's Disease**

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Drosophila melanogaster are the most commonly used species of *Drosophila* in the laboratory. Their use in the modelling of human neurodegenerative disease is predominantly based on the inherent presumption that the fundamental aspects of cell biology are conserved throughout evolution in higher organisms. This is supported by the fact approximately 75% of human disease-related genes have homologs in *Drosophila* [1], suggesting that molecular mechanisms underlying disease in humans may be conserved in the fly.

There are many compelling reasons to studying AD in the fly. The fly brain is estimated to have in excess of 300,000 neurons and, similarly to mammals, is organized into areas with separate, specialized functions such as learning, memory, olfaction and vision. Flies are also highly practical; they have a short generation time (10 days), are inexpensive to keep (although, unlike *C. elegans* and mice, they cannot be recovered alive from freezing) and relatively short lived. Although one could argue the fly's maximum lifespan of 50 - 80 days is significantly greater than that of the worm (~18 days), it is still much shorter than that of the mouse (2 - 3 years), making it ideal for studying a progressive age related disease such as AD.

In addition, the fly has an unrivalled battery of genetic tools, including a fully sequenced genome; an extensive library of mutant stocks including RNA interference (RNAi) and knock out (KO) lines; sophisticated transposon based methods for gene manipulation; systems for spatial- and temporal-specific ectopic gene expression; and balancer chromosomes. Balancer chromosomes are unique composed of multiple inversions that prevent recombination, together with dominant lethal visible and markers. They allow the maintenance in long term culture of lethal or deleterious mutations in heterozygotes, without any necessity to set up specific crosses.

The combination of such extensive genetic tools and practicality makes the fly ideal for genetic screening. A variety of screening methods are available in the fly, involving chemical mutagenesis (EMS), genetic deletion kits or mobile genetic elements (P-, EP-, GS-elements). Genetic screens are powerful experiments providing an unbiased forward genetics approach, which allows the discovery of genes or metabolic pathways not immediately apparent in the pathogenesis of AD.

Life cycle of *Drosophila melanogaster*

The *Drosophila* life history is divided into four distinct morphological phases (See figure 1). Periods of growth and development can be easily distinguished from sexual maturity and the adult phase. Development time from egg to adult is approximately 10 days at 25°C, although this can change depending on the mutant being used. For instance, flies mutant for the insulin receptor substrate protein, chico, typically take 12 days to develop whereas mutants lacking the *Drosophila* insulin-like peptides 2,3 and 5 (dilp 2,3-5) can take up to 18 days to develop [2]. Once fertile eggs are laid, larvae start to emerge around 24 hours later and then enter three distinct stages of growth or instars known as L1, L2 and L3. L1 and L2 last for 24 hours each whereas the L3 stage lasts for 48 hours. During L2 the larvae become larger in size and switch from feeding on the surface of the food to burrowing down into the food. Feeding can last ~100 hours before larvae leave the food medium and crawl up the sides of the vial or bottle to pupariate. The pupal period lasts approximately 4 days, during

which time pupae undergo metamorphosis before eclosion into adult flies. Adult flies consist almost entirely of post-mitotic, fully differentiated cells, with the exception of cells in the gonad and some cells in the gut and Malpighian tubule (fly equivalent of the mammalian kidney), which continue to divide.

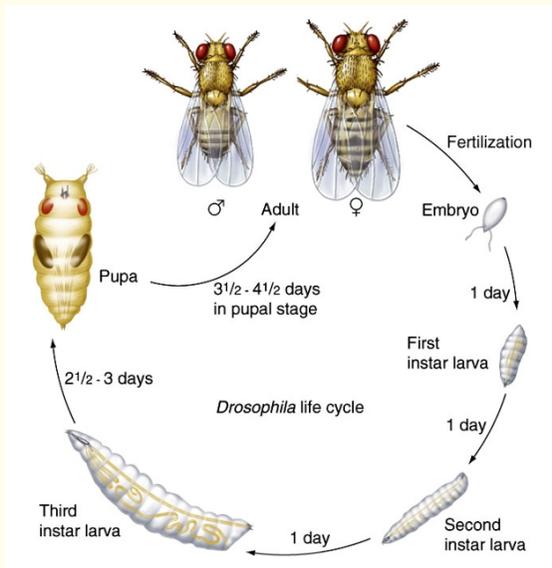


Figure 1: *Drosophila* life cycle: The *Drosophila* life cycle consists of a number of stages: embryogenesis, three larval stages, a pupal stage, and (finally) the adult stage.

Figure adapted from <http://www.easternct.edu/~adams/Drosophilalifecycle.html>

Freshly enclosed flies have shrivelled wings and are pale with a dark spot on their abdomen, as a result of their last feed as L3 larvae. Wings expand within an hour, followed by pigmentation. Female virgin flies will not mate within the first 8 hours post-eclosion. After mating, females commence a heavy egg-laying period that peaks after 5 days post-copulation. Virgin flies also lay eggs but fewer and in a different pattern.

Bibliography

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