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Drosophila Melanogaster as An Organism for Disease Modelling

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Abstract

The use of *Drosophila melanogaster* (fruitfly or fly in short) in biological sciences spans over more than 100 years and its history is a very rich one. It was the fly which helped discover the concept that heritable traits resided on chromosomes and it went on to provide pioneering landmark discoveries in the field of classical genetics. It was initially selected by Thomas Hunt Morgan to understand how organisms underwent changes in order to get selected for the process of evolution. Mass breeding of flies lead to a serendipitous discovery of the *white* mutation and its linkage to the X chromosome whichinitiated the use of fruitflies for genetic research and was accelerated further by Morgan'sstudents Alfred Sturtevant and Calvin Bridges[240 241].

Keywords: Drosophila, model, disease

Introduction: It has helped win Nobel prizes for fundamental discoveries such as the pioneering research done by Ed Lewis on defining the structure of a gene to Eric Weischaus and Christiane Nusslein-Volhard in identifying a significant number of genes involved in the process of embryonic development[242] and recently to Jeffrey Hall, Michael Rosbach and Michael Young for their discoveries of molecular mechanisms that control and regulate circadian rhythms. Thomas Hunt Morgan himself won the prize for discovering the role played by chromosomes in heredity and another scientist named Hermann Muller who was interested in Morgan's work won the prize for the production of mutations inchromosomes with the help of X-rays.

Life cycle and neurobiology:

A single fertile female can lay hundreds of genetically identical eggs which contain the zygote. The egg produces a larva which feeds on the given food, grows through 3 phases termed as instar and gets converted into a pupa. The pupa in turn develops into an adultor imago. The process of the adult coming out of the pupa is known as eclosion. The overall life cycle and the duration of transition from one phase to another is dependent on temperature. At ambient temperature, the time period for completion of the cycle ranges from 8 to 10 days[243]. Each developmental stage is considered as an individual model system and each has its specific advantages. The embryo has been extremely useful in studying certain developmental processes such as cell fate determination, organogenesis, pattern formation, neuronal development and axon pathfinding. The wandering third instar larva is usually used to study certain behavioral patterns and physiological processes due to its near transparent body structure. The adult structures are contained within the larva as imaginal discs and as the larva transitions to the pupal stage these discs undergo huge morphological changes to give rise to mature adult structures. Thus, the study of molecular mechanisms underlying the development of imaginal discs has provided vital insights into embryonic development of both flies and humans. The adult fly is a complex organism having characteristics similar to higher organisms. It has structures which perform functions equivalent to those of the lung, heart, gut, kidney and the reproductive tract of mammals. Its brain has more than lakh neurons forming neuronal circuits which govern complex behaviour such as flight navigation, sleep, circadian rhythms, feeding, courtship, learning, grooming and aggression. Inspite of the many differences between flies and humans, the conserved genes, biology and physiology of the fly brings it to the forefront to study basic biology and disease modelling[242].

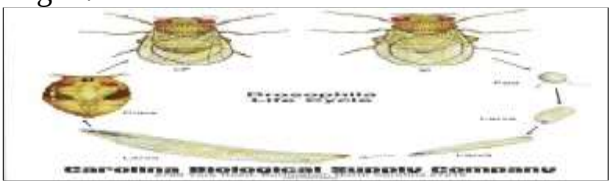

Fig 2.4: Life cycle of *Drosophila melanogaster* (Carolina *Drosophila* manual;www.carolina.com)

With respect to studying PD, certain anatomical and physiological features are conserved between fly and humans. Once neuroblasts start forming neurons in the fly brain and the ventral nerve cord (VNC), the first thing that the axons and the dendrites do is to findtheir targets. Axon guidance is one of the processes highly conserved between the fly and mammals[243]. This process involves undertaking of steps by an extracellular matrix protein, Slit, and its receptor, roundabout (Robo)[244]. The fly has only one gene encoding the protein whereas mammals have multiple genes encoding functional orthologs and operating through the same molecular mechanisms to regulate axon guidance[245]. Another set of extracellular matrix protein and its receptor, Netrin and Frazzled respectively, involved in axon guidance mechanisms are conserved between flies and mammals. Netrin has been shown to be responsible for axon outgrowth and guidance in dopaminergic neurons of mammals[246] and their study in the fly might help understand the formation and circuitry of dopaminergic neurons and the knowledge might assist in unveiling targets for aspects associated with neurobiology and neurodegeneration. The larval system is mainlyused to study motor neuron control of movement and synaptic structure and function both of which are key areas involved in the pathophysiology of PD. The VNC consists of bilaterally symmetrical ganglia corresponding to individual segments and each segment comprises of approximately 400 neurons. Each half of the segment contains 36 motor neurons identified till now which have been found to innervate 30 body wall muscles[243]. The neuropil in the VNC are ensheathed by glia to form a structure similar to the blood brain barrier found in vertebrates. General transmission in the VNC, usually excitatory and input to the motor neurons is mediated by nicotinic cholinergic receptors whereas thefly neuromuscular junction (NMJ) has glutamate and GABA as the primary excitatory and inhibitory neurotransmitters respectively[247].

The function of the synapse is conserved between the fly and humans and its study at the NMJ is informative in elucidating the various mechanisms and processes taking place at the synapse such exocytosis, endocytosis, neurotransmitter release and even plasticity[248 249 250]. Since synaptic vesicle dynamics are greatly affected in PD, *Drosophila* larva NMJ serves as a good modelling alternative in studying how these mechanisms are affected in PD.

The adult visual eye serves as an excellent phenotypic system in neurodegenerative disease modelling. The adult compound eye of *Drosophila* is a repeating hexagonal array of approximately 800 facets (called ommatidium) per eye. Both ommatidia can cover about 85% of the surrounding visual space between them[251]. Each ommatidium comprises of different subsets of cells, one of them being the photoreceptor cells which are actually light sensitive neurons[252]. The entire eye comprises of the retina, lamina, medulla, lobula and lobula plate. The optic lobes on each side of the brain contains between 60,000 and 70,000 neurons[253 254]. The axons from each ommatidium travel from the retina to the optic lobes in a precise map and without this photoreceptor cell axon innervation, the optic lobes undergo a massive degeneration[255 256].

The repeating and precise nature of the eye called the neurocrystalline lattice[257] is vital to detect genetic mutations or certain treatments that might affect the structure and since all neurodegenerative models produce severe defects in the structure of the eye, it is relatively easy to correlate the changes taking place in the eye to those which might be taking place in the brain. The approximately 2,00,000 neurons found in the fly brain form distinct neuronal circuits mapped in detail[253] and govern all fundamental processes and complex behaviours. The neurotransmitters and the molecular mechanisms governing these processes and behaviours are highly conserved with higher organisms. Neurotransmitters present are serotonin, dopamine, glutamate, GABA, acetylcholine,adenosine, histamine and neurokinins, utilizing both G-protein coupled and ionotropic receptor. The fly contains no adrenergic system. The corresponding functions in the fly are instead mediated by the monoamine octopamine.

The fly brain has an important region termed as the protocerebrum which mediates various

aspects of higher order behaviours. One important area of the protocerebrum isthe mushroom body. It comprises of Kenyon cells whose afferent tracts are organizedinto 3 lobes on each side of the brain and these tracts are responsible for mediating olfactory learning and memory. Another important process governed by the protocerebrum is the circadian rhythm taken care by a small group of cells located at the base of the optic lobes. The central complex is another important are of the fly brain comprising of the fan shaped body ellipsoid body[243]. This complex is also involved in regulating higher order behaviours such as learning, courtship and locomotion[258]. The antennal lobes located in the anterior region of the brain is innervated with sensory neurons arriving from the antennae. Output from the antennal lobes innervates the mushroom body making it an important area of the fly brain. The olfactory glomeruli resemble the olfactory cells in vertebrates. Another region, the suboesophogael ganglia takes care of gustatory responses; its neurons receiving sensory afferents from taste neurons distributed throughout the adult fly. It also takes care of feeding behaviour of flies[259 260].

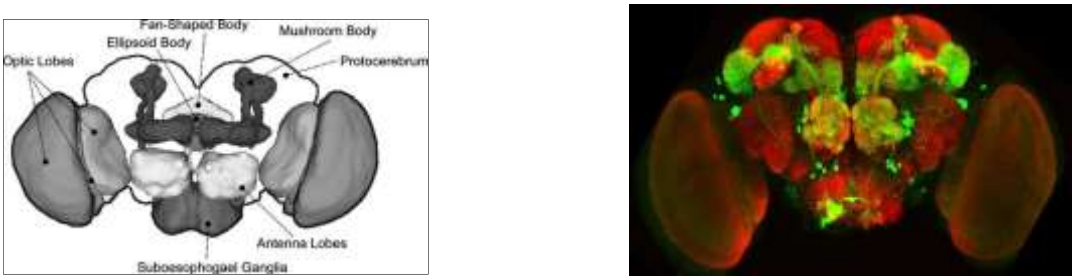

Figure 2.5: Schematic and coloured representation of fly adult brain[243]

Dopaminergic neurons in the fly brain have been traced and mapped using an antibody against tyrosine hydroxylase, an enzyme involved in the dopamine synthesis pathway thankfully present in the fly in combination with TH-GAL4 fly strain[261 262]. Dopaminergic neurons occur in 6 bilaterally symmetrical clusters innervating large areas of the brain. They are anatomically positioned and named: paired posterior lateral 1 and 2 (PPL1 and PPL2); paired posterior medial 1 and 2 (PPM1/2) which are often grouped together because of their close proximity; paired posterior medial 3 (PPM3); paired anterior lateral (PAL), and paired anterior medial (PAM)[263]. There are also some DA producing cells located within the medulla of the optic lobes[262]. Flies express 3 types of DA receptors. Two of them are functional orthologs of the mammalian D1 receptor and are excitatory in nature. The third one is a functional ortholog of the mammalian D2 receptor and is inhibitory in nature. One of the D1-like receptors is exclusively expressed in the mushroom body whereas the second receptor is detected in the mushroom body as well as the central complex[264 265]. A study reported through functional analysis that the D2 receptors might be located in the mushroom body and the antennal lobes but it is not a confirmed data[266]. Synthesis of DA is conserved between *Drosophila* and mammals and besides modulating important behaviours eg. arousal during mating, *Drosophila* DA system is also involved in locomotor control[267 268]. Thus, the loss of DA neurons as occurs in PD affects locomotor control in *Drosophila* as well[269].

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