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TOXICOLOGICAL STUDIES ON MODEL ORGANISM *DROSOPHILA MELANOGASTER*

Mr. Shidagoud Patil
PG (M.sc) Student, Govt Arts and Science College Karwar

ABSTRACT

The fruit fly (Drosophila melanogaster) has long been a premier model for developmental biologists and geneticists. The utility of Drosophila for toxicology studies has only recently gained broader recognition as a tool to elaborate molecular genetic mechanisms of toxic substances. The common fruit fly, Drosophila melanogaster, has been considerably studied for decades. In effect, it was introduced as a decisive model in biology about a century agone. The fly shares several introductory natural, biochemical, neurological and physiological parallels with mammals. It's proved that about 75% of mortal complaint-causing genes have functional homolog in D. melanogaster. The fly can effectively be maintained at low cost in the laboratory, and it has been recommended as an indispensable model to invertebrate operation. Accordingly, it has attracted the interest of toxicologists. In the present review, we presented and bandied the openings available to toxicologists who wish to use D. melanogaster as a model to study neurodegenerative consequences, oxidative stress and antioxidant labels, cancer, inflammation and metabolic diseases. We also included key information similar as the FlyBase resource that will help toxicologists interested in using fruit flies as an indispensable organism to other organism models.

INTRODUCTION

The arthropod Drosophila melanogaster, belonging to the family Drosophilidae, is a dipteran fly (i.e., a member of an order of insects containing true fly). This fly was introduced as a model in biology about 100 times agone and it was decisive for the development of inheritable and affiliated fields (Sepel and Loreto, 2010). This fly has been so far used as a model of genotoxicity, and only later, it has been included as a implicit model for studying systemic toxicology or as an indispensable model for studying toxicology (Dean 1985; Barale 1991; Brusick et al, 1998; Cummings and Kavlock, 2005; Whitworth et al, 2006; Rand 2010; Paula et al, 2013). D. melanogaster displays anatomical features similar to wings and the compound eyes. It can live between 40-120 days based on diet and environmental stress conditions (e.g., temperature and population concentrations).

Diet similar as cornmeal prolongs the lifetime of D. melanogaster, while diets with high amounts of free available carbohydrates (saccharides) and cholesterol can reduce the life span (Hirth, 2010). In addition, densed growth of flies has been shown to reduce the life of the flies (Joshi and Mueller, 1997). The parallels of molecular processes involved in the control of life expectancy and aging between D. melanogaster and homo sapiens, coupled with good degree of inheritable homology between the two species, makes D. melanogaster an intriguing model system for toxicologists. Of particular significance, further, more than 65-70% of human complaint genes are present in D. melanogaster, making it an important model to understand not only how the genes induce conditions, but also the discovery of the relation of similar genes to cause diseases. Compared with other models, D. melanogaster offers speedy generation time, easy to use, and easy to maintain in the laboratory in a large volume due to its short body size and short life span.

D. melanogaster is extensively used as a promising model organism in genetics, biochemistry, cell biology, and experimental biology. Since the last decades, it has been used as a model to interpret diseases concerned with humans, and initially for toxicological studies.

Due to the efficiency achieved in the use of D. melanogaster in developmental biology, it has met the criterias of the European Centre for the Confirmation of alternative methodologies (ECVAM): Reduction, Refinement and Readjusting (3R's) of laboratory organisms operation (Festing etal., 1999). D melanogaster as a model questions many ethical issues and its genome can be fluently manipulated in the study of a particular molecule of interest under a defined condition. Interestingly, the post genomic sequencing of D. melanogaster created a great deal of attention of toxicologists because it revealed functional conservation of many of the genes present in mammals. As a result of this, it has been used to gain mechanistic perceptivity in toxicological studies (Adams etal., 2000). Therefore, its use in toxicological studies will continue to induce precious data.

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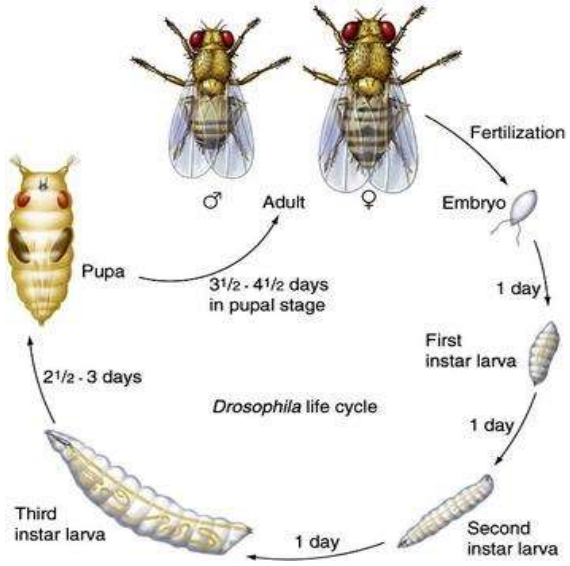

Figure 1
Life Cycle of Drosophila melanogaster

The life cycle of D. melanogaster is speedy because a Fertile parent can induce hundreds of genetically analogous seed at 25 °C within 10 to 12 days (Figure 1). Another intriguing trait of the fly is that it's a multiple model organism. Therefore, its embryo, larva, nymph and adult can be used as models in different toxicological settings. For case, the embryo and the nymph can be used as models in experimental toxicological studies, and the larva is used to study physiological and behavioural characteristics. Interestingly, the adult fly has sophisticated and complex systems. It has structures that can mimic the original functions of mammalian reproductive tract, heart, kidney, gut and lung. Also, the brain of the fly has more than 1 lakh neurons that are important inflight navigation, circadian measures, memory, feeding, courtship and aggression. Importantly, D. melanogaster responds to several central nervous system medicines in a analogous way to mammals (Nichols etal., 2002; Rothenfluh and Heberlein; Satta etal., 2003; Wolf and Heberlein, 2003; Andretic etal., 2008).

In the present mini review, I try to show the use of D. melanogaster as a promising model in toxicology.

DROSOPHILA CULTURE AND MEDIA

In order to include D. melanogaster for toxicological studies, it's important to maintain culture medias of flies for backup since they've a short lifetime. For ease of culturing and transferring of fruit flies, invariant bottles and vials are used. It's also important to fully clean and disinfect the bottles and vials to help prevent outbreak of transmissible agents. There are numerous standard methodologies for D. melanogaster media. In laboratory for case, we usually maintain and rear flies on cornmeal medium (1% brewer's yeast, w/ v 2%, w/ v sucrose; 1%, w/ v powder milk; , w/ v agar;0.08%, v/ w nipagin) at constant temperature and moisture (23 degree C; 60% relative moisture, respctly) under 12 h dark/ light cycle. Li etal. (2007) and Peng etal. (2009) have used rudimentary diets containing 105 g of cornmeal, 21 g of yeast, 105 g of glucose, and 13 g of agar; also,0.4% of Ethyl 4-hydroxybenzoate was added to the diet in order to help mould growth (Hugo and Peter,).

ENDOCRINOLOGY OF D. MELANOGASTER

The endocrine glands of D. melanogaster are deduced from epithelial tissues and, at molecular and cellular conditions, they function in a analogous way to those of vertebrate glands. For case, D. melanogaster possesses circulating hormones, plasma membrane receptors (PMRs) and nuclear receptors (NRs) controlled by the same chemical and natural mechanisms found in the hormonal system of vertebrates. The genome of D. melanogaster codes PMRs and NRs that correspond to different sorts of vertebrate receptors, also including those function in neurotransmission.

D. melanogaster has two major hormonal systems Ecdysone (Ecy, scheme 1B) and Juvenile Hormone (JH, scheme 1D). Ecdysone is a steroid hormone produced in the thoracic glands, and it's homologous to the steroid hormones similar as estradiol produced from cholesterol. Juvenile Hormone is a sesquiterpinoid produced in the corpora allata in the brain of D. melanogaster, and it shares some traits with retinoic acid

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(scheme 1C) (King-Jones and Thummel, 2005). The moult in D. melanogaster is anteceded and controlled by Ecy. The product of JH ceases at the end of the third instar larval stage to allow for the increase in Ecy to initiate pupation, cell death, and the development of new cellular structure. JH latterly returns in the adult stage and controls spermatogenesis, lifetime locomotor , feeding , secondary sexual characters and courtship behaviour. It also interacts with Ecdysone to promote fertility (Helmut et , 2010).

As refocused out above, the regulation of D. melanogaster development shares several chemical and natural features with vertebrates, still, the influence of classical experimental toxicants in vetebrates have been little explored in D. melanogaster (Lee etal., 1989; Carmora et al., 2008; Rand etal., 2010).

DRUG ADMINISTRATION PATHS IN D. MELANOGASTER

Medicines can be administered to D. melanogaster via different paths depending on the type of study, the nature of the medicine and the experimental stage of the D. melanogaster. During the embryonic stage, medicines can be administered by permeabilization (Rand etal., 2010); whereas, in the naiad stage, it can be added to the media in the solid state for long exposures or in a media containing yeast paste for shorter duration exposure. In the adult flies, multitudinous routes of exposure are available (Figure 2). Still, If the medicine is unpredictable for example if it is volatile, it can be administered as a vapour using suitable vehicle like ethanol (Moore etal., 1998). The medicine can also be mixed with the diet of the D. melanogaster in a defined ratio, or using some filters impregnated with the medicine in the presence of sucrose (Nichols etal., 2002). Some experimenters prefer to administer certain medicines to the D. melanogaster by fitting the medicines directly into the exposed nerve cord of flies (Torres and Horowitz, 1998), or directly into the tissue in order to speedy diffusion in the cells of the D . melanogaster (Dzitoyeva etal., 2003). The taste of the medicine should be taken into consideration before administering the medicine, because the fruit flies tend to avoid medicines with aversive taste (Ja et , 2007). The common method in this case, is to mix the medicine with substrates that taste well similar like that of a sucrose or yeast paste, or to starve them for some period before exposure. It's mandatory to carry out pilot studies to examine different ratios of concentrations with different duration of exposure. In our laboratory, we occasionally carry out survival graph experiments using different concentrations of the medicines to help in choosing the varied doses of the medicines to be used, and the duration of exposure. Sometimes, we use different vehicles too for certain medicines to choose the efficient vehicles with the medicines. In our studies, we concluded that corn oil (2.5%) isn't a good vehicle for introducing 4- vinyl cyclohexene (VCH) in the rudimentary diet (unpublished results), indeed though it had been used as vehicle in mouse models. This is because the mortality recorded in the control fruit flies(corn oil) was analogous to the VCH- treated groups. The reason for food toxicity of corn oil wasn't delved, but flies typically can tolerate up to 1% of fat in the diet (Miquel et , 1982). And Ethanol gave greater results when used as vehicle with the fruit flies at final ratio of 2.5%. Indeed, D. melanogaster can tolerate up to 5% of ethanol in their diet, but they do prefer diets containing lower ratios of ethanol (3-4%).

Another system to be used in exposing fruit flies to medicines that have aversive taste is to starve the fruit flies for 17 hours, and also transfer the D. melanogaster to the vial containing the medicine for 5-6 minutes, so that the fruit flies can fleetly consume the medicine. This strategy can help to snappily determine the acute effects of the medicine. Generally, if the fruit flies are maintained on food impregnated with the medicine for longer than 24 hours, it allows for a steady state to be achieved in the fruit flies, still, it has some disadvantage of possible adaptive mechanism due to longer exposure and also due to down or up regulation of targeted genes in the drug administration routes.

AREAS OF APPLICATIONS TO USE FRUIT FLIES IN TOXICOLOGICAL STUDIES

1. The use of D. melanogaster in assessing oxidative stress and antioxidant bio-markers.
2. The use of D. melanogaster in neurodegenerative disorders.
3. As a model organism to study cancer.
4. D. melanogaster can also be used to study cardiovascular diseases.
5. Use of fruit flies in the study of inflammation and infections.
6. D. melanogaster can be used to assess metabolic disorders.
7. D. melanogaster in the study of diabetes.

CONCLUSION

Conclusively, it's important to take into account implicit differences in pharmacokinetics and pharmacodynamics which may deduce differences in medicine and tissue distribution status between mammals and D. melanogaster, when applying toxicological data from D. melanogaster to mammals. For case, in toxicological studies that includes the central nervous system, there may be differences in blood- brain permeability (Mayer etal.,). In addition, despite the fact that there's a strong correlation of toxicity between the D. melanogaster and the mammals, metabolic differences may be present in which some drugs may cause toxicity in D. melanogaster and not in humans (Rand, 2010). Still, this supposition can be applied to all experimental involving human toxicology, despite of this the use of fruit flies in toxicology must be encouraged to determine common or universal routes or targets of any toxicant or class of toxic agents. In effect, the establishment of routes in simple organism models that could be used as early “complex molecular targets” that could assess the implicit toxicity of drugs in mammals which would be important from both economical and ethical point of view. In this case, the exploration using simple organism models similar as worms (Caenorhabits

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elegans) and insects (particularly fruit flies) should be farther sti (Leung etal. 2008; Rand, 2010; Li etal. 2013; Rodrigues etal. 2013) to fete which pathways should be considered originally in the toxicological studies.

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