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Review

From fat fruit fly to human obesity

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HIGHLIGHTS

- We reviewed recent *Drosophila* models of human obesity.
- We highlight the fruit fly methods in the studying of energy homeostasis.
- The use of *Drosophila* screens can identify novel obese-related genes and therapeutics.
- *Drosophila* provide an excellent model to study feeding behavior and energy balance.

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ABSTRACT

Obesity is a chronic metabolic disease that has become a global problem. Although a tremendous amount of effort has been spent to prevent and treat obesity, its etiology is still largely unknown and there are not yet sufficient strategies to control obesity. Recently, the fruit fly, *Drosophila melanogaster*, has become a useful model for studying metabolic homeostasis and obesity related disorders. The goal of this mini-review is to summarize the recent achievements of *Drosophila* models and to highlight the experimental protocols used in studying feeding behavior and energy homeostasis in the fly. The *Drosophila* models provide useful tools to understand obesity pathogenesis and to develop novel therapeutics.

Contents

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1. Introduction

Obesity is a chronic metabolic disease that has become a global problem. The World Health Organization (WHO) reported that there were about 1.4 billion overweight adults, 500 million obese adults, and 40 million overweight children in 2011 (www.who.int). The prevalence of childhood obesity has increased up to 15% recently and the risk of obesity co-morbidities also increased at an alarming rate [1,2]. Although the etiology of obesity is not fully clear, a lifestyle including inappropriate diet and exercise habits, genetic factors, and an 'obesogenic' environmental are the major contributing factors. Great effort is needed to investigate the molecular mechanisms controlling food intake and body weight and to develop novel pharmacological and non-pharmacological strategies to combat obesity. The fruit fly, *Drosophila melanogaster,* has become an excellent model for studying nutrient-sensing pathways and metabolic homeostasis in a cost-effective and expedient manner [1–3]. Recent studies from *Drosophila* models of diabetes and obesity illustrate that the molecular mechanisms underlying energy balance in *Drosophila* are largely conserved between humans and flies. This mini-review highlights the advantages of the experimental protocols of *D. melanogaster* in the study of feeding behavior and energy homeostasis. For other aspects of *Drosophila* work related to metabolic disorders, there are several recent excellent reviews [3–17].

2. General biology of *D. melanogaster* related to metabolism

The advantages of using *Drosophila* are the low cost of maintenance and rapid developmental course in the fly compared with rodents or other mammal models. The majority of disease-causing genes and fundamental physiological processes of *Drosophila* are conserved in humans. *D. melanogaster* can be used to mimic the pathogenic condition of human disorders to identify pathways and novel drug targets by taking advantage of available genetic tools. Moreover, *D. melanogaster* can be used to screen and validate small molecules for drug discovery.

The fly genome contains four chromosomes and encodes about 14,000 genes. About 75% of disease-associated genes in humans have functional orthologs in the fly [18,19]. The fly life cycle includes four developmental stages: the embryo, the larva, the pupa, and the adult, and is very rapid compared with that of mammals. At room temperature, one pair of mating flies can produce hundreds of offspring within ~12 days.

Each developmental stage of *Drosophila* has its own specific advantages and can be used as a model system to study metabolic homeostasis. The embryo can be used to study fundamental development by assessing organogenesis, cell fate determination, pattern formation, neuronal development, and axon path finding. The larva, especially the third instar larva, and the pupa stages can be used to investigate various developmental and physiological processes, fat and sugar storage, as well as some behaviors such as foraging, feeding, and locomotor activity. The fly has various organs with functions similar to those of the mammalian gut, lung, heart, kidney, and reproductive tract. There are more than 100,000 neurons in flies that form neuronal circuits to regulate various behaviors, including feeding, circadian rhythms, sleep, learning and memory, mating courtship, grooming, aggression, and flight navigation [20].

Drosophila digestion and neuroendocrine systems are very conserved in vertebrates. Food is digested and absorbed in the crop and midgut, which is the fly counterpart of the stomach and intestine [21]. The key metabolic regulating organs in flies include fat bodies (functions as white fat tissue and liver), Malphigian tubules (functions as kidneys), oenocytes (functions as hepatocyte-like cells), and pars intercerebralis–corpora cardiac system (functions as the hypothalamus–pituitary system) [1,21–24]. These organs integrate information on environmental changes and internal metabolic status, and coordinate physiological activities to maintain energy homeostasis [1]. Glycogen and lipids are stored in the fly fat bodies [24]. The biochemical pathways for controlling sugar and fat storage [58] are also very similar to those in human. In flies, the IPCs (insulin producing cells) in the pars intercerebralis function similarly to pancreatic β-cells. The corpus cardiaca functions like the pancreatic α-cells and have been shown to be involved in adipokinetic (AKH) secretion. AKH is similar to mammalian glucagon. The pars intercerebralis–corpora cardiaca system of a fly receives information on the internal metabolic status and coordinates the physiological and behavioral activities of various peripheral organs [22]. Thus, *Drosophila* models can be used to investigate various aspects of energy balance including feeding control, food perception, energy expenditure, and lipometabolism.

3. Genetic tools for studying energy homeostasis

Since the full genome of *D. melanogaster* was sequenced [25], it has tremendously affected the fly world and elevated its role as a model to study human biology and diseases. *Drosophila* research is considered to be at the forefront since many novel discoveries of genes, proteins, cellular pathways, and genetic concept and tools are often identified first in the fly and then validated later in mammalian models. One of the unique benefits of using the *Drosophila* system is that various genetic tools and stock collections are available [59]. Here, we highlight the utility of these genetic tools and describe their application to metabolic research.

3.1. Using Gal4/UAS system to regulate gene expression [26]

The principle of the UAS/Gal4 system is that the yeast transcriptional activator Gal4 can specifically bind to the upstream activated sequence (UAS) resulting in expression of the recombinant genes cloned downstream of the UAS sites in a tissue specific manner. Tissue-specific Gal4 driver fly lines are available in various stock centers (e.g. Bloomington Center, Indiana University, USA) for many tissues [20,27]. For metabolic studies, the most frequently used driver flies are shown in Table 1 [37]. The UAS/Gal4 system can lead to overexpression or mis-expression of any gene, and can assess any resulting