

PROGRESS

Drosophila and the genetics of the internal milieu

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'Homeostasis', from the Greek words for 'same' and 'steady', refers to ways in which the body acts to maintain a stable internal environment despite perturbations. Recent studies in *Drosophila* exemplify the conservation of regulatory mechanisms involved in metabolic homeostasis. These new findings underscore the use of *Drosophila* as a model for the study of various human disorders.

In 1865, Claude Bernard, in his *Introduction to the Study of Experimental Medicine*, proposed the concept of the 'internal milieu', later referred to as 'homeostasis' in 1932 by Walter Cannon. Homeostasis is one of the most remarkable properties of complex systems that permit organisms to function effectively in a broad range of environmental conditions and allow survival against fluctuations such as temperature, salinity, acidity and nutrients. The kidney, for example, contributes to homeostasis by maintaining salt and ion levels in the blood, regulating the excretion of urea, reabsorbing substances into the blood and regulating blood water levels. Homeostasis depends on the dynamic action and interaction of a number of sensors to adapt to ever-changing environmental conditions, and on hundreds of positive and negative feedback mechanisms.

In recent years, and perhaps surprisingly, we have learned, mostly from genetic studies of physiological responses in *Drosophila*, that many parallels exist between invertebrate and mammalian homeostasis. As exemplified by the seminal studies of Vincent Wigglesworth¹, insects have historically been long-standing models in physiology as a result of their technical advantages such as short life cycles, large populations and the possibility of simple surgical procedures. In the past, however, interest in their physiology was driven mostly by intellectual fascination with their diverse physiological adaptations to virtually every habitat on Earth, as well as by potential applications for pest control. Here we review several recent findings that establish *Drosophila* as an emerging model for mammalian physiology.

Metabolic homeostasis

Drosophila and all other higher organisms constantly adapt their energy needs to nutritional status through metabolic regulation; that is, sugar and lipid homeostasis. The emerging picture in the fly is that of a simpler and well-balanced integrated system between various organs, each with distinct physiological roles in maintaining energy homeostasis (Fig. 1). *Drosophila* has a less complex genome than vertebrates and has little gene redundancy. For example, flies have a unique insulin receptor that mediates all functions that have so far been attributed to insulin-like peptides. Sugar levels are maintained by neurosecretory cells located in the brain and ring gland (together forming a bipartite '*Drosophila* pancreas') that secrete insulin and adipokinetic hormone (AKH, the insect glucagon) into the open haemolymph (the '*Drosophila* blood')²⁻⁵ (reviewed in refs 6-8). Excess sugar is stored in the form of glycogen that accumulates both

in muscles and in the fat body (the '*Drosophila* liver'). On stimulation by AKH, the fat-body glycogen phosphorylase is activated and sugar (trehalose in insects) is released into the haemolymph. The fat body also acts as the storage place for fat and thus is reminiscent of the 'white fat' of vertebrates. A recent series of studies illustrate the convergences in the control of lipid metabolism between flies and mammals. When food is scarce, fat is released from the fat body into the haemolymph and is then captured by the oenocytes (the fly 'hepatocytes') for energy production⁹. In both systems, information on energy shortage is relayed by lipolytic hormones, which activate a pathway dependent on cyclic-AMP-dependent protein kinase that leads to the activation of specific lipases at the surface of intracellular lipid droplets. However, in flies the specific role of these lipases is still unclear: both adipose triglyceride lipase (*ATGL*) knockout mice and *brummer* (the *ATGL* orthologue in flies) mutant flies are obese as a result of an impairment of lipid mobilization^{10,11}.

Genetic ablations have had major roles in deciphering the elaborate crosstalk between the various sensor tissues and their responsive organs. For example, ablation of insulin-producing cells leads to diabetic flies and, conversely, flies in which AKH-producing cells have been ablated have low levels of circulating sugars^{3,12}. Further, proper mobilization of fat from the fat body is perturbed in the absence of oenocytes—an interaction reminiscent of the crosstalk between hepatocytes and adipocytes in humans^{9,13}. Additional

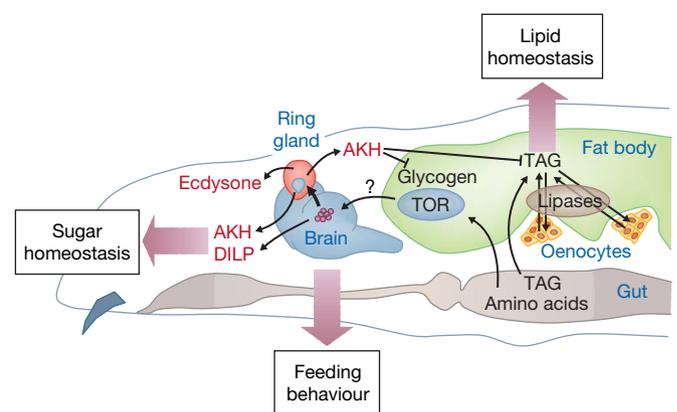


Figure 1 | Interactions between the various organs involved in metabolic homeostasis in a *Drosophila* larva. Hormone names are shown in red, tissue names in blue. DILP, *Drosophila* insulin-like peptides; TAG, triacylglycerol.

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insights have been obtained from the use of drugs such as sulphonylurea (glyburide or tolbutamide), currently used in the treatment for type 2 diabetes as activators of insulin secretion by pancreatic beta cells¹⁴. *Drosophila* larvae fed with sulphonylurea show increased sugar levels, suggesting that AKH-expressing cells in the fly use a conserved mechanism for coupling circulating sugars to glucagon and AKH release⁴.

An important notion emerging from studies in the fly is that all tissues in the organism might not be exposed or equally sensitive to variations in nutritional conditions. The fat body, in particular, seems to be a unique metabolic sensor because it has a pivotal function in buffering nutritional information for the entire animal^{15–17}. For example, in conditions of amino-acid restriction, the conserved TOR pathway in fat cells functions as an energy sensor that induces a remote and systemic inhibition of insulin/insulin-like growth factor signalling, leading to a general decrease in growth during larval development¹⁶.

Cross-regulation between tissues for the control of insulin signalling is reminiscent of recent observations in mammals related to insulin resistance, which leads to obesity and type 2 diabetes, two components of a highly prevalent and complex disorder called the metabolic syndrome^{18,19}. Whether *Drosophila* is a good model for dissecting the basic molecular and genetic mechanisms of this disorder is still uncertain; however, the first example of insulin-resistant flies has emerged recently. Teleman *et al.*²⁰ showed that flies that do not express the microRNA-encoding gene *miR-278* in the fat body are lean and have elevated levels of sugar in the haemolymph, despite high expression levels of insulin. Further, whereas injection of insulin into wild-type larvae provoked an activation of the insulin pathway in fat cells, this response was abrogated in *miR-278* mutant animals, indicating that the 'lean fly' phenotype is associated with insulin resistance in the fat body²⁰. These findings are reminiscent of the decreased fat-pad mass observed in the fat-specific insulin receptor knockout model in the mouse²¹. Thus, as in mammals, insulin signalling in *Drosophila* regulates patterns of energy storage in fat and other tissues, and disruption of this process by insulin resistance leads to important lipid disorders.

Interaction between metabolism and other processes

In addition to progress in our understanding of the logic of metabolic homeostasis in the fly, important advances are being made in our knowledge of the complex interactions between metabolism and growth, ageing or behaviour. For relevant reviews in the *Drosophila* literature see refs 22–25. How organisms adapt their growth programme to changes in energy needs and status, and how hormonal systems such as insulin and steroid hormones interact with metabolic regulation, are areas of particular interest for future research. In particular, functional interactions recently identified between insulin and the steroid hormone ecdysone^{26,27} suggest that fly steroids also participate in metabolic control. Further, in adult flies a decrease in metabolic rates resulting from dietary restriction or decreased insulin signalling results in extension of the normal lifespan (reviewed in refs 23, 24). The mechanism by which dietary restriction controls lifespan is unclear, but metabolic studies in this short-lived model system will undoubtedly contribute to an explanation of the control of ageing by nutrition.

Finally, several complex behaviours are modulated by metabolic conditions. Feeding behaviour is regulated by two major intermingled controls: the homeostatic and the hedonic systems²⁸. Homeostatic regulation of feeding ensures that circulating nutrient levels are sensed, which in turn directly regulates feeding activity. Work on *Drosophila* and studies on the mouse recently showed that a TOR-dependent molecular sensor for amino acids exists in specific brain cells (hypothalamic cells in the mouse; neuroendocrine cells in *Drosophila*). These cells sense variations in circulating amino-acid levels and in turn regulate feeding^{29,30}. Understanding the circuits that transmit these neuroendocrine signals is of prime interest for

the study of eating disorders and are beginning to be studied in *Drosophila*²⁵.

Concluding remarks

The goal of this review is to provide a selective overview of recent progress in studies of metabolic homeostasis in *Drosophila*. Through the examples cited, it is clear that many questions will be answered in the next few years. For example, studies will decipher the specific crosstalk between various larval and adult tissues for the control of energy homeostasis. Characterization of mutants associated with insulin resistance is likely to provide insights into the mechanisms of insulin response and its disruption. In addition, *Drosophila* has great potential as a model system in which to study the balance between lipid storage and lipolysis, a process whose disruption in humans leads to obesity or type 2 diabetes.

In flies, the characterization of homeostatic regulatory mechanisms is facilitated by the smaller number of homeostatic constants and, of course, the ever-improving arsenal of available genetic tools. Genetic screens have already identified new components of metabolic regulatory networks (such as *meltd*, a new modulator of FOXO and TSC2 activity³¹), whose function can now be tested in mammals. Genome-wide RNA-mediated interference (RNAi) screens, both in tissue culture cells³² and *in vivo*³³, provide unique tools for the study of metabolic regulations. In particular, *in vivo* RNAi, allowing the activity of a specific pathway to be reduced in a given tissue, should showcase *Drosophila* as a model for metabolic disorders. These *Drosophila* models should prove to be very powerful for drug screening, to determine modes of drug action, and to identify drug targets. Finally, a better characterization of *Drosophila* metabolites will benefit the continuing work to understand experimental perturbations of the 'internal milieu'.

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