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***Review:***

# Recent advances in the neural regulation of feeding behavior in adult *Drosophila*[*]

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**Abstract:** The ability to maintain metabolic homeostasis is a key capability critical for the survival and well-being of animals living in constantly changing environments. Metabolic homeostasis depends on neuromodulators, such as biogenic amines, neuropeptides, and hormones, to signal changes in animals' internal metabolic status and to orchestrate their behaviors accordingly. An important example is the regulation of feeding behavior by conserved molecular and cellular mechanisms across the animal kingdom. Its relatively simple brain coupled with well-characterized genetics and behavioral paradigms makes the fruit fly *Drosophila melanogaster* an excellent model for investigating the neuromodulatory regulation of feeding behavior. In this review we discuss the neuromodulators and neural circuits that integrate the internal physiological status with external sensory cues and modulate feeding behavior in adult fruit flies. Studies show that various specific aspects of feeding behavior are subjected to unique neuromodulatory regulation, which permits fruit flies to maintain metabolic homeostasis effectively.

**Key words:** Feeding behavior; *Drosophila melanogaster*; Neuromodulatory regulation; Internal status; Sensory processing
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## 1 Introduction

Animal species have evolved diverse behaviors to coordinate growth, development, and survival. These behaviors are plastic and are constantly adapted to their internal energy needs and environmental conditions. Neuromodulators, such as neurotransmitters, neuropeptides, and endocrine hormones, play a key role in altering the morphological and/or functional characteristics of neural circuits to achieve behavioral plasticity. In this review, we focus on the feeding behavior of *Drosophila melanogaster*, with an emphasis on how neuromodulators convey internal metabolic needs and external contextual cues to regulate feeding circuits.

## 2 Modulation of feeding behavior

The feeding behavior of the fruit fly is a complex process that includes motivational and sensory components (Pool and Scott, 2014). The motivational component serves to monitor the energy changes in the fly's internal physiological status, and generates a sensation of hunger when stored energy falls below a certain threshold. The hunger signal then promotes food consumption (Dethier, 1976; Edgecomb et al., 1994). Therefore, the motivational component of feeding behavior can be characterized as a quantity

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checkpoint. In parallel, the sensory component detects the taste valence, nutrient value, and textual features of prospective food sources and permits actual food intake (Dus et al., 2011; Koç et al., 2013; Freeman and Dahanukar, 2015; Joseph and Carlson, 2015). Therefore, the sensory component can be characterized as a quality checkpoint of feeding behavior.

### 2.1 Motivational control of feeding

The motivational component of feeding control involves the central nervous system (CNS) and different peripheral tissues (Fig. 1). These two intermingled systems ensure that the internal nutrient level is accurately and promptly monitored, which in turn ensures appropriate regulation of feeding behavior.

The CNS monitors systemic energy storage and alters feeding probability accordingly. When food is scarce, with diminished energy, flies gradually develop a sense of hunger. Recent studies revealed a specific group of CNS neurons expressing SLC5A11, a putative sodium/solute co-transporter-like protein in *D. melanogaster*, as a hunger sensor (Dus et al., 2013; Park et al., 2016). These neurons monitor the depletion of energy stores. As a result, the activity of SLC5A11$^{+}$ neurons is significantly enhanced in hungry flies. Flies with these activated SLC5A11 neurons exhibit increased preference for nutritive sugar. Another group of neurons, named taotie, located in the pars intercerebralis (PI) region, are also identified as internal nutritional sensors (Zhan et al., 2016). They exhibit increased activity in hypoglycemia status and further evoke strong feeding behavior. It is reasonable to speculate that multiple hunger sensors work coordinately to ensure the detection of internal energy storage, which is critical for the survival of adult flies.

Similarly, multiple peripheral tissues can also sense changes in the internal nutritional status and

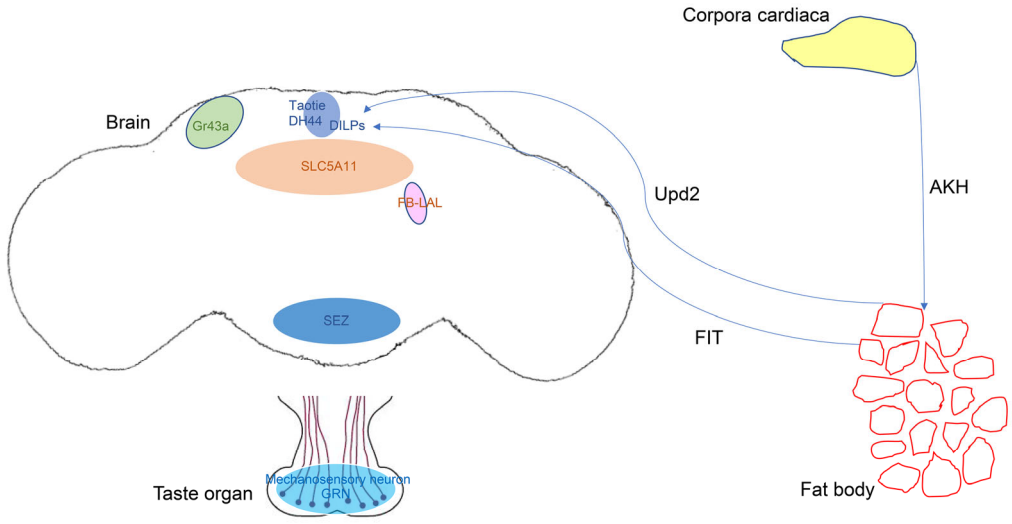


**Fig. 1 Cross-talk between the various organs involved in energy metabolic homeostasis in *Drosophila***

Representation of the fruit fly's neuromodulatory circuits for nutritional signal processing. Metabolic status is directly detected by central neurons. Taotie neurons in the pars intercerebralis region and SLC5A11 (solute carrier family 5 member 11) neurons in the ellipsoid body are activated by hunger signals and evoke feeding behavior. Gr43a neurons in the posterior superior lateral protocerebrum region and DH44 (diuretic hormone 44) neurons in the pars intercerebralis region detect internal nutritive sugar levels and regulate the food ingestion process. FB-LAL (fan-shaped body-lateral accessory lobe) neurons in the posterior medial protocerebrum region sense protein deficiency and promote protein intake. Physiological state is also reported by peripheral tissues. Unpaired 2 (Upd2) is released from the fat body in response to dietary nutrients and promotes *Drosophila* insulin-like peptide (DILP) secretion indirectly to regulate feeding behavior. FIT (female-specific independent of transformer) is another peptide released from the fat body in response to protein-specific satiety and regulates DILP secretion to suppress protein intake. Adipokinetic hormone (AKH) secretion from the corpus cardiaca cells is stimulated by low energy levels, which in turn mobilizes energy storage and regulates locomotor activity. In addition to the nutrient sensors mentioned above, gustatory receptor neurons (GRNs) and mechanosensory neurons in the taste organs detect different characteristics of tastants, and the subesophageal zone (SEZ) serves as a general taste relay center that conveys taste representations to the downstream motor neurons to drive food intake. Both processes contribute to the maintenance of metabolic homeostasis in *Drosophila*

stimulate various feeding decisions. In particular, the fat body works as a metabolic sensor (Géminard et al., 2009). As a functional counterpart to mammalian liver and adipose tissue, it monitors internal carbohydrate and lipid levels and produces humoral signals, such as Unpaired 2 (Upd2). Upd2, a secreted cytokine, conveys metabolic status to insulin-producing cells (IPCs) in the brain, via a population of GABAergic neurons (Rajan and Perrimon, 2012). When flies are in a starved condition, the transcripts of Upd2 decrease and the secretion of *Drosophila* insulin-like peptides (DILPs) is reduced. The down-regulation of DILPs triggers flies to display motivated feeding behavior.

The corpus cardiacum is another important endocrine tissue in the fruit fly that releases endocrine signals representing the internal nutritional status (Kim and Rulifson, 2004). Adipokinetic hormone (AKH) is one of the key hormones released by corpus cardiaca cells. In fasted conditions, these cells sense low levels of circulating sugars and stimulate AKH selection. AKH not only mobilizes stored glycogen and fat in the fat body to maintain nutritional levels in the hemolymph, but also modifies specific aspects of feeding behavior, such as promoting sustained food seeking in food-deprived flies (Lee and Park, 2004; Bharucha et al., 2008). In a sense, AKH is the functional analog of mammalian glucagon, which is also triggered by starvation and promotes a variety of hunger-induced processes (Isabel et al., 2005; Grönke et al., 2007).

### 2.2 Sensory control of feeding

The sensory component of feeding control involves gustatory neurons, interoceptive neurons, and mechanosensory neurons in the peripheral nervous system (Dahanukar et al., 2007; Weiss et al., 2011; Miyamoto et al., 2012; Dus et al., 2015; Sánchez-Alcañiz et al., 2017; Scott, 2018). The properties of potential food sources are therefore evaluated in multiple parallel pathways. These pathways play an essential role in identifying palatable, nutritious substances and avoiding harmful or even toxic compounds.

Flies sample prospective food with gustatory neurons, which are distributed on the legs, the labial palp of the proboscis labellum, internal mouthpart organs, the margins of the wing, and the gustatory-like organs on the female ovipositors (Stocker, 1994). Gustatory detection usually starts with activation of gustatory neurons on the legs and the proboscis labellum. There is an old philosophical saying "Calorie-rich sugars taste good; organisms are nourished by the sweet; bitter taste elicits rejection." Indeed, flies are attracted to sweet taste. In contrast, they have an aversive response to bitter taste. So, sweet and bitter are the two basic tastes that flies use to guide their food choice.

The sweet taste of sugars is exclusively mediated by a family of eight gustatory receptors (Gr5a, Gr61a, and Gr64a–f) (Dahanukar et al., 2001, 2007; Ueno et al., 2001; Thorne et al., 2004; Jiao et al., 2007, 2008; Slone et al., 2007; Fujii et al., 2015). These receptors are co-expressed in sugar-responsive neurons. Specifically, Gr5a, Gr64a, and Gr64f receptors are required for detecting almost all kinds of available sugars. Among them, Gr5a and Gr64a are tuned to different sugars. Gr5a participates in the response to trehalose and melezitose (Dahanukar et al., 2001, 2007; Ueno et al., 2001), while Gr64a responds primarily to sucrose and maltose (Dahanukar et al., 2007; Jiao et al., 2007). In addition, Gr64f works as a co-receptor that is needed for the detection of almost all sugars (Jiao et al., 2008).

The mechanism underlying bitter taste detection is not fully described. Though more than 30 gustatory receptors are presumed to be bitter receptors, the functional profiles of only a few have been characterized. Gr32a, GrR33a, and Gr66a are expressed in all bitter gustatory sensory neurons and are required for the responses to large numbers of bitter compounds (Lee et al., 2009, 2010; Moon et al., 2009; Weiss et al., 2011). In contrast to these three broadly tuned receptors, other receptors may be responsive to only a limited number of tastants. For example, Gr8a is narrowly tuned to L-canavanine, and Gr93a to caffeine (Lee et al., 2009, 2012).

In addition to these two canonical taste qualities, there is accumulating evidence that flies can also use their gustatory neurons to sense other nutritional compounds, like amino acids and fatty acids. Ir76b is an inotropic chemosensory receptor that is expressed in some specific gustatory neurons. These $Ir76b^{+}$ neurons are required to elicit appetite for amino acids (Chen and Dahanukar, 2017; Ganguly et al., 2017; Steck et al., 2018). In addition, attraction to fatty acids is mediated by another set of gustatory neurons

expressing different inotropic chemosensory receptors (IR25a, IR76b, and IR56d) (Ahn et al., 2017).

Flies can also detect the nutritive content of food sources, in parallel to the function of peripheral gustatory receptor neurons (GRNs). Different clusters of specialized interoceptive neurons can directly sense various circulating macronutrients. There is growing evidence that these CNS neurons stimulate the intake of nutritive foods and prevent the consumption of nutritionally imbalanced foods. One example of these internal nutrient sensors is Gr43a. A cluster of Gr43a-expressing neurons in the posterior superior lateral protocerebrum are activated by a surge of fructose from ingested food and promote further feeding (Miyamoto et al., 2012). Another set of interoceptive neurons expressing diuretic hormone 44 (DH44) promote ingestion of dietary nutritive sugars (Dus et al., 2015). These neurons are selectively activated by nutritive sugars, such as glucose, fructose, and trehalose. Flies with activated DH44-expressing neurons show a robust increase in feeding behavior.

Dietary protein can also be sensed independent of taste responses. Besides nutritive sugars, $DH44^{+}$ neurons have also been identified to directly sense dietary amino acids and induce food consumption (Yang et al., 2018). The activity of these neurons is selectively activated by specific amino acids (L-glutamate, L-alanine, and L-aspartate) in a manner that requires putative amino acid transporters (CG13248 and CG4991). Essential amino acid-deficient (EAAD) food rejection is mediated by a group of dopaminergic central neurons. When ingesting EAAD food, GC nonderepressing 2 (GCN2) kinase is activated by uncharged transfer RNAs (tRNAs) to trigger an intracellular signal that leads to increased dopamine release, resulting in diminished feeding (Bjordal et al., 2014).

Last, but not least, the food preference of flies is also affected by textural features of food. Two key physical characteristics of food, hardness and viscosity, are sensed by md-L (multidendritic neurons in the labellum) mechanosensory neurons that express transmembrane channel-like (TMC) protein. These neurons extend elaborate dendritic arbors innervating the bases of taste hairs and exhibit directional selectivity in response to mechanical stimuli (Zhang et al., 2016). Another subset of mechanosensory neurons supply additional evidence for the fruit fly's ability to discriminate food texture. These neurons detect food texture via no mechanoreceptor potential C (NOMPC), a member of the transient receptor potential (TRP) family mechanosensory channel (Sánchez-Alcañiz et al., 2017).

### 2.3 Nutrient feeding

Beyond sensing the general hunger status and consuming adequate food to satisfy their caloric needs, flies can also detect the deprivation of specific nutrients (aka "metabolic hunger") and ingest the desired nutrients to meet their internal needs (Ribeiro and Dickson, 2010; Vargas et al., 2010; Walker et al., 2015; Liu et al., 2017).

Maintaining protein homeostasis is a well-studied example. Protein is a major type of dietary nutrient and plays essential roles in multiple physiological processes, such as egg laying. Mating induces an increase in the egg laying of female flies (Ribeiro and Dickson, 2010; Tian and Wang, 2018). Since egg production is heavily protein consuming, mated flies have a greater drive for protein intake. This reproductive status-dependent food preference relies on the function of the sex peptide, a class of proteins produced by males and transferred to females during copulation. The sex peptide then acts on a small group of sensory neurons in the female reproductive organ to modulate food intake and yeast preference (Carvalho et al., 2006; Ribeiro and Dickson, 2010). Long-term protein deficit can induce a compensatory protein appetite, mediated by a small cluster of dopaminergic neurons (Liu et al., 2017). These two protocerebral posterior medial 2 (PPM2) dopaminergic neurons in each brain hemisphere undergo branch-specific plastic changes in the presynaptic terminals. As a result, their downstream signaling via the DopR2 receptor in the FB-LAL (fan-shaped body-lateral accessory lobe) neurons is modulated to promote protein intake. Conversely, in protein-sated flies, a protein-specific satiety hormone female-specific independent of transformer (FIT) is released by the fat body to suppress further protein consumption (Sun et al., 2017). Therefore, the consumption of dietary protein is well maintained at multiple levels.

Besides dietary proteins, adult flies may also need other types of essential nutrients for survival and reproduction, including vitamins, minerals, and lipids (Piper et al., 2014). Whether the nervous system of

flies can also assess their internal adequacy and modulate specific food intake behaviors is an important yet largely overlooked question.

## 3 Various components of feeding behavior and their regulation

The fruit fly's feeding behavior is composed of a hierarchical series of food seeking and consumption subprograms. These behavioral components are highly flexible and subjected to various regulations by satiety status and metabolic needs. Notably, subprograms of the feeding behavior are not always regulated in a coordinated manner by the upstream neuromodulatory system, but rather are independently controlled by multiple delicate neuromodulatory cues. Significant advances have been made towards understanding how specific actions of feeding behavior are finely tuned by various modulators.

### 3.1 Seeking food

In an energy deficient condition, flies initiate food seeking as their first subprogram of feeding behavior. The pursuing flies show two obvious behavioral characteristics in this specific period.

Firstly, starved flies exhibit enhanced locomotor activity, which may facilitate their exploration of the surrounding environment and enhance their chances of encountering and locating potential food sources. Previous studies have highlighted the importance of AKH and octopamine signaling in starvation-induced hyperactivity (Isabel et al., 2005; Yu et al., 2016).

In a food-deprived status, flies show an incremental increase in locomotor activity. Ablating AKH-producing cells eliminates starvation-induced hyperactivity (Lee and Park, 2004; Isabel et al., 2005). Downstream of AKH, octopamine and octopaminergic neurons have been shown to be both necessary and sufficient for starvation-induced hyperactivity (Yang et al., 2015). Blockade of these octopaminergic neurons in fasted flies eliminates enhanced locomotor activity, while activation of these same neurons promotes locomotor activity in fed flies. Amazingly, though octopaminergic neurons are broadly distributed in the fly brain, only a small set located in the subesophageal zone (SEZ) is sufficient for starvation-induced hyperactivity (Yu et al., 2016). These neurons co-express the receptors of AKH and satiety hormone DILPs, which in turn constantly integrate hunger/satiety signals. In this manner, flies are capable of adapting locomotor activity to their internal energy status (Yu et al., 2016).

The second component of food seeking is to locate prospective food sources and to direct the locomotor behavior of flies.

### 3.2 Locating food sources

Starved flies also need to locate desirable food sources accurately and quickly. To this aim, such flies show functionally reconfigured olfactory and gustatory processing of food-associated cues to optimize their detection of prospective desirable food (Kim et al., 2017).

It starts with a shift in their perception of attractive and aversive stimuli in the olfactory system. Starved flies exhibit increased synaptic outputs from $Or42b^+$ olfactory receptor neurons (ORNs) that mediate odor-guided attraction, as well as decreased synaptic outputs from $Or85a^+$ ORNs that mediate odor-guided aversion (Root et al., 2011; Ko et al., 2015). This functional remodeling of $Or42b^+$ ORNs and $Or85a^+$ ORNs is mediated by small short neuropeptide F (sNPF) signaling and tachykinin signaling, respectively. Note that a general satiety signal, the DILPs, regulates the expression levels of sNPF and tachykinin receptors, therefore influencing the remodeling of the olfactory circuitry by starvation. Low insulin signaling in starved flies leads to higher expression of sNPF receptor in Or42b ORNs and tachykinin receptor in Or85a ORNs.

Additionally, starvation shapes the gustatory circuitry of flies to ensure efficient food locating. When starved, flies show increased sensitivity of sweet-sensing GRNs that express the Gr5a receptor and decreased sensitivity of bitter-sensing GRNs that express the Gr66a receptor (Inagaki et al., 2012, 2014; Marella et al., 2012; LeDue et al., 2016). This reciprocal regulation of attractive and aversive gustatory sensitivity allows starved flies to accept a range of potential food sources that they would otherwise ignore or reject when fed ad libitum. In starved flies, the enhanced sugar sensitivity requires *Drosophila* neuropeptide F (dNPF) and dopamine signaling (Inagaki et al., 2012, 2014; Marella et al., 2012). The dNPF-expressing neurons act upstream of dopaminergic neurons to promote the release of dopamine onto Gr5a neurons. Conversely, the decreased bitter

sensitivity is mediated by AKH, sNPF, γ-aminobutyric acid (GABA), and octopamine pathways (Inagaki et al., 2014; LeDue et al., 2016). AKH acts genetically upstream of sNPF-expressing neurons to trigger sNPF release and the subsequent activation of a subset of GABAergic neurons. As a result, the activity of octopamine (OA)-ventrolateral (VL) neurons that release octopamine is reduced and the synaptic output from Gr66a neurons that express octopamine receptor is thus attenuated. Taken together, at the levels of both olfactory and gustatory inputs, starved flies become more sensitive to appetitive cues and less sensitive to aversive cues, increasing their capability to locate, occupy, and acquire food sources.

### 3.3 Food ingestion

Once potential food has been found and assessed, starved flies initiate the food consumption subprogram. During food ingestion, flies constantly evaluate their internal energy status and the value of ingested food for a proper termination of food ingestion.

Proboscis extension reflex (PER) is often the first step of appetitive behavior, immediately followed by food ingestion. Upon ingestion, food is brought into contact with specific GRNs located in the pharynx (LeDue et al., 2015; Joseph et al., 2017; Murata et al., 2017). The axons of pharyngeal gustatory neurons project into the SEZ, the taste center of the fly brain to which other peripheral GRNs send their axons. This projection pattern raises the possibility that the pharyngeal taste system functions as a secondary food quality sensor that operates on a short timescale right after the initiation of food ingestion.

This hypothesis is supported by accumulating evidence. Eight pharyngeal gustatory neurons co-expressing Gr43a and Gr64e are activated by the ingestion of palatable sugar, which in turn provides a positive feedback signal to prolong ingestion (LeDue et al., 2015). Remarkably, a cluster of twelve cholinergic interneurons located in the SEZ, named IN1 neurons, have been shown to selectively receive signals from pharyngeal gustatory neurons (Yapici et al., 2016). Sucrose ingestion elicits a persistent activation state in IN1 neurons in starved flies, which leads to sustained ingestion. In contrast, as the starved flies progressively become satiated, the response to sucrose is attenuated in IN1 neurons, which results in decreased ingestion. Surprisingly, a pair of pharyngeal gustatory neurons expressing IR60 have been revealed to restrict sucrose ingestion. This is suggested to prevent a hyper-fast influx of sugar (Joseph et al., 2017). Collectively, the rapid regulation of food ingestion by pharyngeal neurons can help to optimize feeding behavior at an early stage.

Sensory signals from the mouthparts and the pharynx are essential for equilibrated food intake. However, food ingestion is not a simple sensory-motor reflex. Numerous higher-order processes are also required for the modulation of ingestion. For example, although we have emphasized SLC5A11, taotie, Gr43a, and DH44 neurons as nutritional sensors, they also play a role in promoting food ingestion in starved flies (Miyamoto et al., 2012; Dus et al., 2015; Park et al., 2016; Zhan et al., 2016). Besides these regulators, additional higher-order modulators have been identified that modulate different aspects of food ingestion. Leucokinin signaling selectively regulates meal termination (Al-Anzi et al., 2010). Mutations in the genes encoding leucokinin or leucokinin receptor cause an increase in meal size, and ablation of neurons expressing these genes has a similar effect. However, overall food ingestion does not alter due to an associated reduction in meal frequency. Another anorexigenic neuropeptide is allatostatin A (Hergarden et al., 2012). Allatostatin A-expressing neurons respond to satiety signals and suppress both feeding initiation and food ingestion. In addition, four GABAergic interneurons establish a central feeding threshold that is not affected by sensory signals and metabolic status (Pool et al., 2014). This essential inhibitory control acts genetically upstream of E49 and MN11 motor neurons to suppress meal initiation and intake.

In addition to the inhibitory mechanism that operates on the neurons in the brain, food ingestion is negatively regulated by gut filling, through posterior enteric neurons expressing PPK1 ion channels (Olds and Xu, 2014). As the fly continues to ingest food, the level of mechanical tension is relayed to the brain via activation of these neurons. Once the extent of mechanical tension reaches a certain level, food ingestion is likely to terminate. The exact sensing mechanism of these $PPK1^{+}$ neurons remains unclear. It is also of interest to explore whether different compartments in the digestive system, such as the crop, foregut, and midgut, play different roles in sensing digestive food and the modulation of food ingestion.

## 4 Conclusions

Feeding helps to acquire a desirable and balanced dietary input for energy and nutrient homeostasis, which is vital to the evolutionary fitness of animals. It is subjected to intense regulation by multiple neuromodulatory systems. Here, we illustrate recent progress in understanding neuromodulation in the feeding behavior of adult flies, which links various internal energy and nutrient needs to adaptive behaviors. We highlight the sophistication of individual steps in feeding behavior that can be independently adjusted by neuromodulatory cues. The fruit fly shares the basic metabolic regulation that is conserved throughout evolution, so as a simple genetic model it will provide reliable insights to advance studies in more complex vertebrates, and to enhance understanding of specific feeding-related neurological and metabolic disorders in humans.

### Contributors

Gao-hang WANG wrote the first draft of the manuscript. Li-ming WANG revised and edited the final version. Both authors read and approved the final manuscript.

### Compliance with ethics guidelines

Gao-hang WANG and Li-ming WANG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by either of the authors.

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## 中文概要

**题　目：果蝇成虫进食行为神经调控的研究进展**

**概　要：**现代社会很多人受到肥胖、代谢紊乱和饮食不调的困扰，我们迫切地需要解决这些严重影响人类生活的问题，但直接在人类中开展研究的方式进展比较缓慢。幸运的是人类的进食和代谢过程与其它高等动物甚至昆虫相似，都具有极高的保守性。因此，我们可以利用相对容易操作的低等生物作为研究对象，加快解决问题的进程。果蝇便是一种非常好的实验对象，它是一种神经系统比较简单的模式生物。本文对果蝇成虫的进食行为进行了详细阐述，强调了果蝇的神经系统能实时监控机体的代谢状态，并能将其与外界环境的食物信号精准整合，从而调节它们进食的每个步骤。通过对果蝇进食和代谢相关的神经调节的研究能拓宽我们对人类相应疾病研究的视野。

**关键词：**进食行为；果蝇；神经调节；代谢状态；感知信号传递