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# Effects of specific amino acids on the metabolism of *Drosophila melanogaster*

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**Abstract**: To investigate the perception and effects of specific amino acids on animals, we took *Drosophila melanogaster* as a model organism, measured the dietary preference and uptake of 20 amino acids as well as detected the effect of different amino acids on adult motility. We found that male and female *Drosophila* preferentially sense and consume different amino acids, and threonine specifically affects the motility of adult females. We then fed the third instar larvae with four dietary conditions (starvation, threonine, sucrose, and threonine + sucrose) and analyzed the differentially expressed genes between groups by transcriptome profiling. Gene Ontology annotation and Kyoto Encyclopedia of Genes and Genomes pathway analysis revealed that threonine affects steroid hormone and redox signaling. We further validated 8 genes by real-time fluorescence quantitative PCR in both larvae and adults, and found that the biological responses of threonine may depend on developmental stages. Our findings lay a foundation for additional in-depth investigation of the sensing and metabolic regulation of specific amino acids and provide clues of its molecular mechanism at the gene expression level.

**Keywords**: amino acid metabolism; *Drosophila melanogaster*; dietary preference; threonine; transcriptome profiling
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## 1 Introduction

Amino acids are nutrients with essential metabolic functions[1]. Different amino acids play unique roles in many biological processes due to their functional diversity and metabolic complexity. For example, tumor cells have special dependence on glutamine, and glutamine metabolism inhibitors become potential anticancer drugs[2]; tryptophan metabolism is a main regulator of the immune response, and inhibitors of its metabolic enzymes have entered clinical trials as anticancer drugs[3]; arginine deprivation is considered as a potential treatment for various tumors with arginine metabolism defects[4]; branched amino acids are highly correlated with cardiovascular diseases and type II diabetes mellitus[5]; leucine, arginine, and glutamine directly activate mTOR signaling[6]. However, special functions of individual amino acid under different physiological or pathological conditions have yet to be identified.

In recent years, *Drosophila melanogaster* has become an important genetically tractable model in nutrition and metabolism research due to its similarities with mammalian[7]. The primary anatomical structures of fruit fly are similar to the mammalian system, including the brain, peripheral nervous system, heart, lung (fly trachea), kidney (fly Malpighian tubules), adipose tissue (fly fat body), intestine, and gonad[8-10]. At the molecular level, *Drosophila* and mammals also share the core metabolic signals, including Insulin, Glucagon, Leptin, cytokines, EGF, TNF, Myostatin, TGF-beta, Hedgehog, and other signal molecules that play an important role in metabolic regulation[13-15].

Therefore, *Drosophila* model has made many important contributions to the understanding of biological functions of special amino acids: in fasted *Drosophila* larvae, leucine and isoleucine directly activate IPCs to release DILP2 and DILP5[16]; in third instar larvae, Class IV peripheral neurons respond to the loss of environmental arginine via Slif [17, 18]; in adult flies, threonine promotes adult fly sleep by specifically inhibiting GABA neurons in the brain[19], while starvation-induced upregulation of serine synthesis inhibits sleep through cholinergic neurons[20]; glutamate, alanine, and aspartic acid can directly stimulate DH44 neurons through the putative amino acid transporter *CG*13248 to increase food consumption in

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*Drosophila*[21]; methionine restriction extend the lifespan of fruit flies in a low-protein state[22], but methionine uptake stimulates the proliferation of intestinal stem cells by promoting the synthesis of S-adenosylmethionine (SAM) in intestinal cells [23]. Nevertheless, whether particular amino acid plays unique roles in many other biological processes still need to be explored.

To fully understand the effects of specific amino acids on development, metabolism, and nutrient perception of *Drosophila*, we tested the dietary preference and uptake of different amino acids and detect their effect on adult motility and identified threonine as the primary target. We then fed the fast-growing third instar larvae with four different dietary conditions and analyzed the differentially expressed genes by transcriptome profiling (RNA-seq) and validated by real-time fluorescence quantitative PCR (RT-qPCR). Our research deepens the understanding of the connection between specific amino acids and animal nutrition perception and metabolic regulation and paves the way for further in-depth study.

## 2 Experimental

### 2.1 Materials

Amino acids (MACKLIN, China); Blue Food dye (Hongda, China); Agarose (Sangon Biotech, China); Sucrose (Biofroxx, Germany); PBS buffer (Sangon, China); 96-well ELISA plate (Thermoscientific, American); Trizol reagent (Invitrogen, American); Goldenstar RT6 cDNA Synthesis Mix (Tsingke, China); Tsingke Master qPCR Mix-SYBR (+UDG) (Tsingke, China); RT-qPCR primers (General Biotechnology, China) and sequences are shown in Table1.

**Table 1.** Primer sequences of RT-qPCR.

| Gene Name | Sequence |
|---|---|
| RPL23 | F:GACAACACCGGAGCCAAGAACC<br>R:GTTTGCGCTGCCGAATAACCAC |
| Alp4 | F:CAACGTGGACAAACAAGTGCC<br>R:ATGGCTCCGTAATGGGTTTTC |
| CG10814 | F:ATCTGCCACAGACACTGAGTA<br>R:CGGACCACTCTATACACAGGA |
| CG11842 | F:GAGAATGGCGAGGTGGAATGG<br>R:TCCTTGTGGTGAGTAGTGGCA |
| CG14089 | F:ATGAGGACGAGTATGATTACGGC<br>R:CGGATTTCTGCGTTCACTAAAGG |
| Prx2540-1 | F:ATGATCCTGCCCACTGTCAC<br>R:CAGTGGTGCGGACGTAGTTT |
| CG42815 | F:CAACCACCTCTACCACGACC<br>R:CTGCGCCGATGTATCCTTCT |
| CG32071 | F:GCAGGGAACGAAGAGACGAA<br>R:CTCACAATGCGTTCACCGTC |
| CG33012 | F:GTTACCGATGGGATAGATCCTGA<br>R:GTGAGTAGTACCATTCCAGTTGC |

### 2.2 Fly stocks

*w*1118 flies were used for all assays. All flies were reared and maintained on standard cornmeal food at the room temperature.

### 2.3 Dietary preference test

After eclosion, flies were mated freely for 4 d, then starved on 1% Agarose plate for 24 h and fed with various amino acids for 1 h. X-shaped 4-compartment cultural plates were used: the first and third quadrants of the experimental plates contained 1% Agarose, the second and fourth quadrants contained 25 mmol/L amino acid +1% Agarose +1% blue dye; in control experiment, the second and fourth quadrants of the control plates were filled with 1% Agarose +1% blue dye. Experiment setup was performed similarly as previously described[24] (shown in Figure 1(a)). 6 Males or females were kept on the feeding plate for 1h, and then put into an EP tube, homogenized in 300μL PBS buffer and centrifuged at 12000 r/min for 5 min after grinding. Protein concentration and dye concentration in the supernatant were determined by $OD_{280}$ and $OD_{620}$ absorptions on an absorption spectrometry. The influence of the fly size was normalized by dividing $OD_{620}$ by $OD_{280}$. Each experiment was performed with at least three biological replicates. The measurement of preference index is shown in Figure 1(b).

### 2.4 Food uptake test

Food compositions tested: amino acid (25 mmol/L) + 1% Agarose+1% blue dye, amino acid (25 mmol/L) +5% sucrose +1% Agarose, 5% sucrose +1% Agarose +1% blue dye and 1% Agarose+1% blue dye. 8 flies were fed for 10 min. Then the protein and dye concentration were determined by absorption spectrometry. The starvation group was used as a control to normalize the fold change of food uptake.

### 2.5 Locomotor ability assay

Adult flies 4 d after eclosion were fed on the same foods as the food uptake test. The locomotor assay of flies was evaluated by rapid iterative negative geotaxis assay as previously described[25]. The assay is to tap the flies onto the bottom of the tube and calculate the percentage of flies climbing over the marked line over a given time (Figure 3(a)). 8 male or female flies were tested every 24 h. Climbing was documented by video with 2 frame/s. Number and time of flies passing through the marked line were manually quantified.

### 2.6 High-throughput transcriptome sequencing

Early third instar larvae were isolated and fed with four dietary conditions (starvation, 25 mmol/L threonine, 5% sucrose, and 25 mmol/L threonine + 5% sucrose) for 24 h. 30 larvae were lysed in 500 μL Trizol reagent and stored at −80 ℃ till library preparation. The samples were sent to the Igene Book Biotechnology

company (Wuhan, China) for RNA-sequencing. Three biological replicates were prepared.

### 2.7 Real-time fluorescence quantitative PCR

Early third instar larvae and female adults after 4 d post eclosion were fed with 4 kinds of food for 36 h. Total RNA from 30 larvae or 10 adults was extracted by Trizol reagent, and then reverse transcribed into cDNA for RT-qPCR analysis. Three biological replicates were performed for each experiment, and the ΔΔCt method was used for the statistical analysis.

### 2.8 Statistical analysis

Statistical analyses were performed using Microsoft Excel and R program. t-tests performed are 2-tailed non-paired sample with equal variance. Log-rank test was used for the climbing test. All results were presented as means ± S. E. M. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$. Adjusted $p$-value was used for test of significance across multiple samples by the BH (Benjamini-Hochberg) method.

## 3 Results and discussions

### 3.1 Dietary preference of *Drosophila melanogaster*

To understand the effect of nutrient perception of different amino acids, we first test the dietary preferences in adult male and female *Drosophila*. Before the formal experiment, we conducted a preliminary experiment to prove the effectiveness of the test assay (Figure 1(c)). The dietary preferences of *Drosophila* for different amino acids are shown in Figure 1(d). Overall, the adults show preference to several amino acids, suggesting that there is a general positive regulating circuit controlling the amino acid consumption. Females display more robust preference to amino acids than males: females show significant preferences for threonine, glutamine, alanine, and cysteine, but males have no obvious preference for amino acids, suggesting that females are more sensitive in amino acid perception. This observation is consistent with the fact that female need to consume protein diet particularly to reproduction. However, the molecular mechanism of this amino acid preference still needs to be explored.

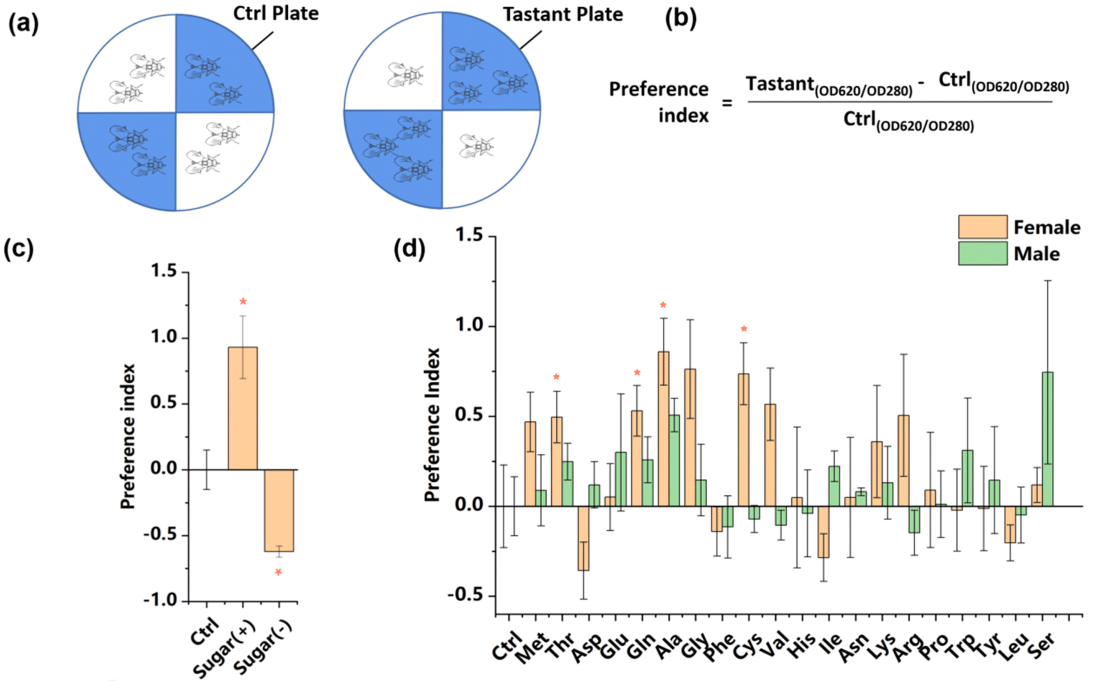



**Figure 1.** Dietary preference of Drosophila. (a) Schematic diagram of dietary preference assay. The X-shaped petri dish was divided into four quarters. In Control Plate, all four quarters contain 1% agarose, with two quarters containing additional 1% blue dye. In Tastant Plate, two quarters contain 1% agarose, and the rest two quarters contain 1% agarose, 1% blue dye, and tested substance with indicated concentration. (b) The formula for calculating preference index. The amount of blue dye ingested was determined using OD620 absorption on a spectrophotometer. Dye uptake was normalized against the total protein (determined by OD280 absorption) to eliminate the influence of fly body size variation. (c) Experiment on dietary preference of Drosophila towards and against sugar. In the Sugar (+) group, 5% sucrose was mixed with 1% agarose containing 1% blue dye in the Tastant group. In the Sugar (−) group, 5% sucrose was added in the 1% agarose without blue dye. (d) Dietary preference of adult male and female Drosophila. Two-choice preference test between 1% Agarose and 1% Agarose with different amino acids (25 mmol/L, a saturated solution was used for amino acid with low solubility). More than 3 biologically replicates were conducted for each condition.

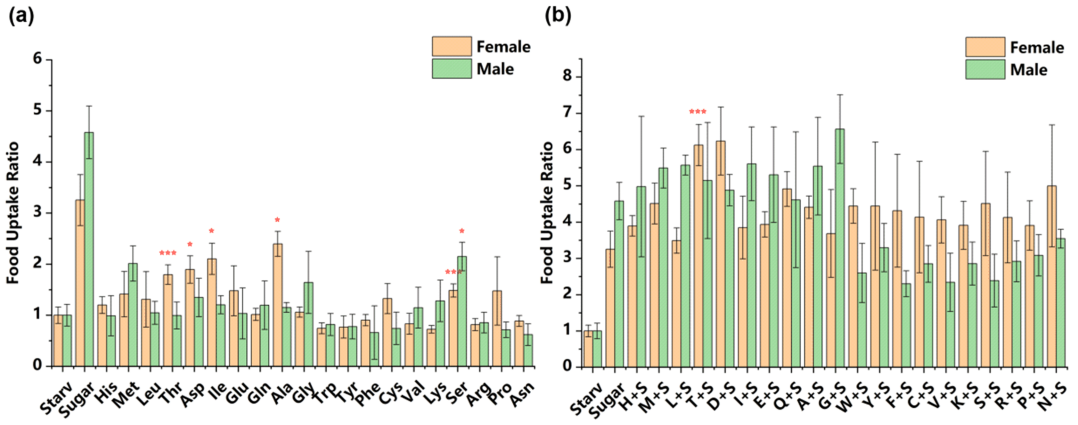



**Figure 2.** Food uptake of adult male and female Drosophila. (a) Food uptake of different amino acids (25 mmol/L). (b) Food uptake of different amino acids (25 mmol/L) with sucrose (5%). Food Uptake Ratio: the average value of OD620/OD280 of the experimental group divided by the Starvation group. More than 3 biologically replicates were conducted for each condition. Saturated solutions were used for amino acids with low solubility. Statistical significance for (b) is calculated by comparing amino acid + sucrose with sucrose alone.

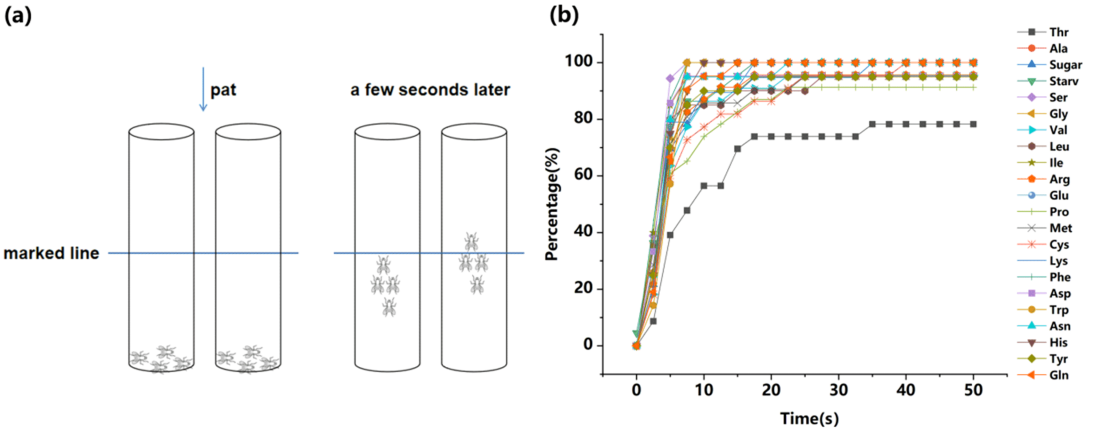



**Figure 3.** Test of the motility of *Drosophila*. (a) Cartoon illustration of the locomotor assay. (b) The locomotor ability of female adult *Drosophila* after 48 h feeding with different amino acids (25 mmol/L, a saturated solution was used for the amino acid with low solubility). More than 20 adult flies were tested counted for each condition.

### 3.2 Food uptake of different amino acids

Considering the total food uptake of *Drosophila* may be regulated by the internal energy or metabolic state of substances, it is necessary to measure the total food uptake under different conditions. Generally, females consume more food than males, as they bear the more energy-demanding tasks of reproduction. Consistent with previous observation, females prefer foods with amino acids more robustly than males: threonine, aspartic acid, isoleucine, and alanine significantly increase food uptake in females but not in males (Figure 2(a)). Only serine promotes food consumption in both sexes.

As the amino acid uptake of *Drosophila* may be affected by material and energy metabolism status controlled by sugar. We also tested the food uptake of different amino acids mixed with sucrose. Interestingly, only threonine significantly increase food uptake in presence of sugar (Figure 2(b)), indicating that threonine may have specific significance for the metabolism of females.

### 3.3 Effects of amino acids on motility

The locomotor ability of flies reflects general fitness, which is frequently used to assay for food toxicity. After feeding 24 h, the motility of males and females under varying nutrition did not change palpably. Interestingly, after 48 h, the locomotor ability of females fed on threonine is significantly reduced (Figure 3(b), Log-rank test significance $p<0.01$). While there is no significant difference in males, which may be due to reduced food consumption than females. Our data suggest that uptake of threonine has a unique effect on females.

### 3.4 RNA-seq and analysis of differential expressed genes

To investigate the metabolic effect of threonine and its downstream signals, we fed early 3rd instar larvae with four different diets and profiled the corresponding transcriptome. We chose larvae instead of adults because larvae are rapid growing stages which make them more sensitive to nutrient changes in diet: adult flies can survive on sugar only diet; in contrast larvae stop development in absence of amino acids in their food. In addition, majority of the previous nutrient study as well as transcriptome profiling used fly larvae rather than adult. Therefore, using larvae for RNA profiling study may maximize the effect of amino acids as well as generate datasets more comparable with previously published ones.

#### 3.4.1 Gene expression between groups

The differential gene expression patterns between feeding sucrose (designated as Sugar) and threonine + sucrose (designated as Thr-Sugar) groups are relatively similar, while starvation (designated as Starvation) and feeding threonine (designated as Thr) groups are more alike (Figure 4(a)). The number of differentially expressed genes (DEGs) between Thr-Sugar and Thr groups is the largest, while almost all the DEGs between Thr and Starvation groups are up-regulated (Figure 4(b)).

#### 3.4.2 Pathway enrichment of DEGs

To compare the enrichment of DEGs in specific pathways, we carried out the Kyoto Encyclopedia of Genes and Genomes pathway (KEGG) analysis. We annotated all the DEGs of different groups by KEGG and then classified the KEGG terms that can be annotated. As we expected, pathways related to the metabolic processes were enriched. The DEGs in Thr-Sugar vs Sugar, and Thr and Starvation groups are enriched in amino acid metabolism (Figure 5(a,b)). The DEGs between Sugar vs Starvation and Thr-Sugar vs Thr groups are related to more energy metabolism, environmental information processing, and cellular processes, consistent with the fact that sugar is an more important metabolic regulator (Figure 5(c,d)). These all prove the validity of our experiment and imply that threonine has a strong impact on the amino acid metabolism pathway of *Drosophila*.

#### 3.4.3 Gene Ontology enrichment analysis

To further study the function of these DEGs, we performed Gene Ontology (GO) enrichment analyses of the top 20 terms with the smallest *p*-values. All genes with significant changes, including both up and down-regulated genes, were used for DEG analysis. Genes involved in catabolism of lipids and triglycerides are enriched in the DEGs between Sugar and Starvation groups, which is consistent with previously discovered starvation- and sugar-induced genes (Figure 6(a,b))[26]. Interestingly, in presence of sugar, Thr addition uniquely triggers changes in nuclear hormone signaling, including ecdysteroid metabolic process, 3-beta-hydroxy-delta 5- steroid dehydrogenase activity, steroid biosynthetic process, suggesting a special function of threonine in developmental regulation (Figufe 6(c)). In contrast, comparison between Thr and Starvation results genes enriched in iron permease complex, reductive iron assimilation, and peroxiredoxin

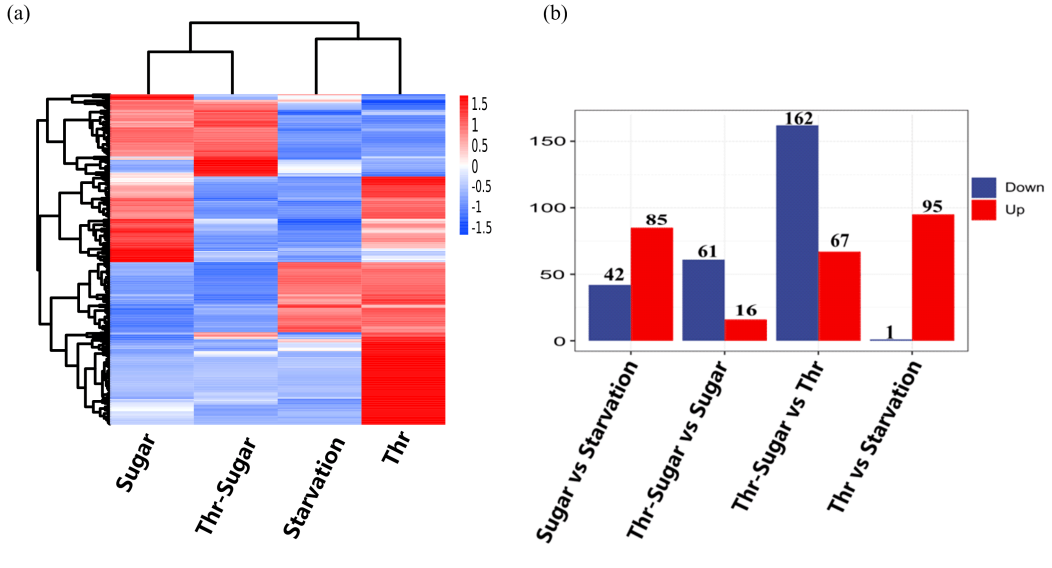



**Figure 4.** DEGs of 3rd instar larvae. (a) Heatmap of differential gene expression profiles in $\log_2$ scale. Dendrograms show hierarchical clustering of different genes. (b) Number of genes significantly altered between groups. False discovery rate (FDR) of 0.05 was used to define the significantly changed genes.

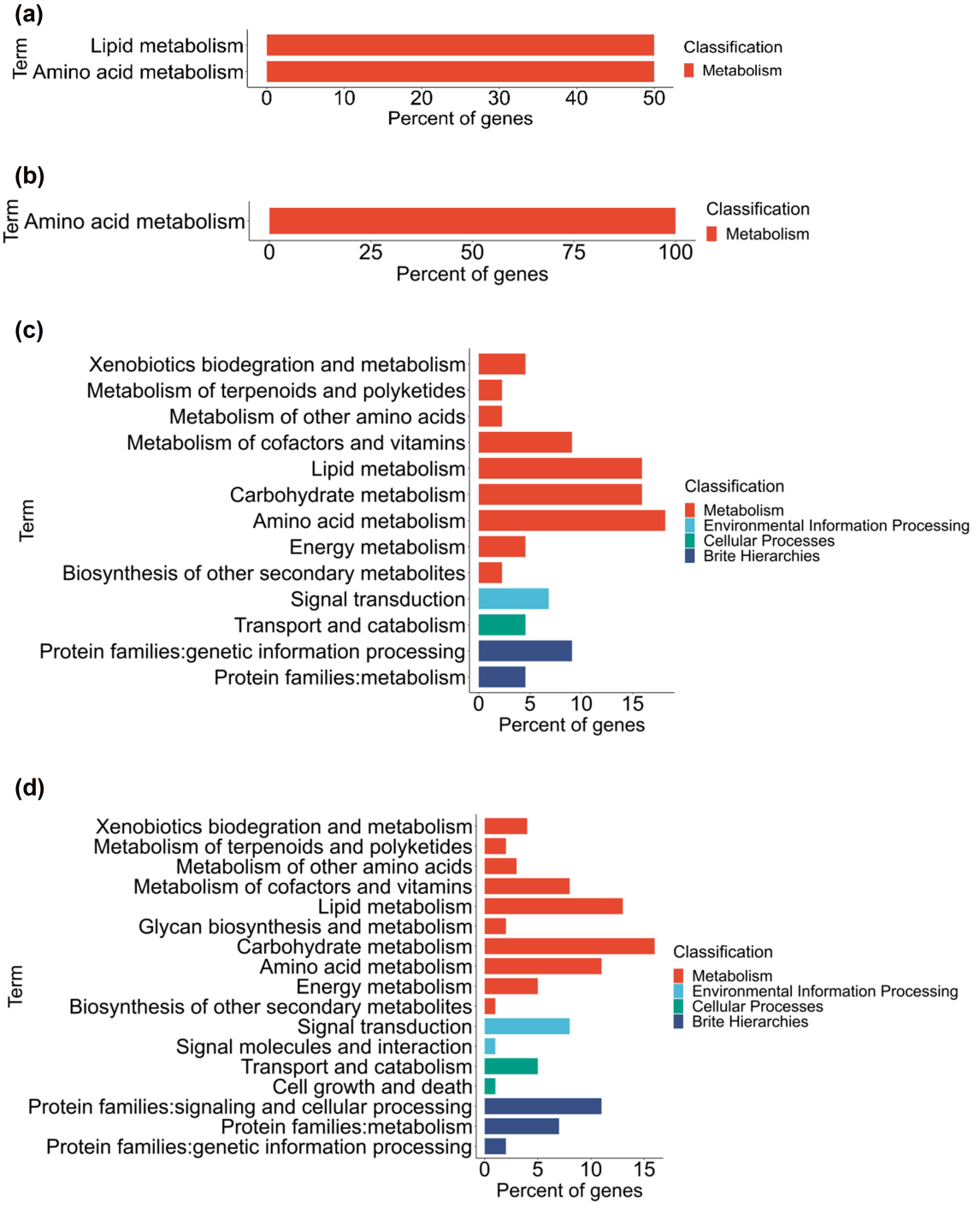



**Figure 5.** KEGG annotation classification of DEGs. (a) Thr-Sugar vs Sugar. (b) Thr vs Starvation. (c) Sugar vs Starvation. (d) Thr-Sugar vs Thr. All genes with significant changes, including both up and down-regulated genes, were used for DEG analysis.

activity, suggesting that the iron-related redox signaling is likely to be specifically affected by threonine (Figure 6(d)). The enrichment of tube development further indicates that changes may happen in morphogenesis. Threonine affects the development and iron ions transport of larvae. This is an interesting result, which has not been reported before. However, the specific molecular regulation mechanism remains to be studied.

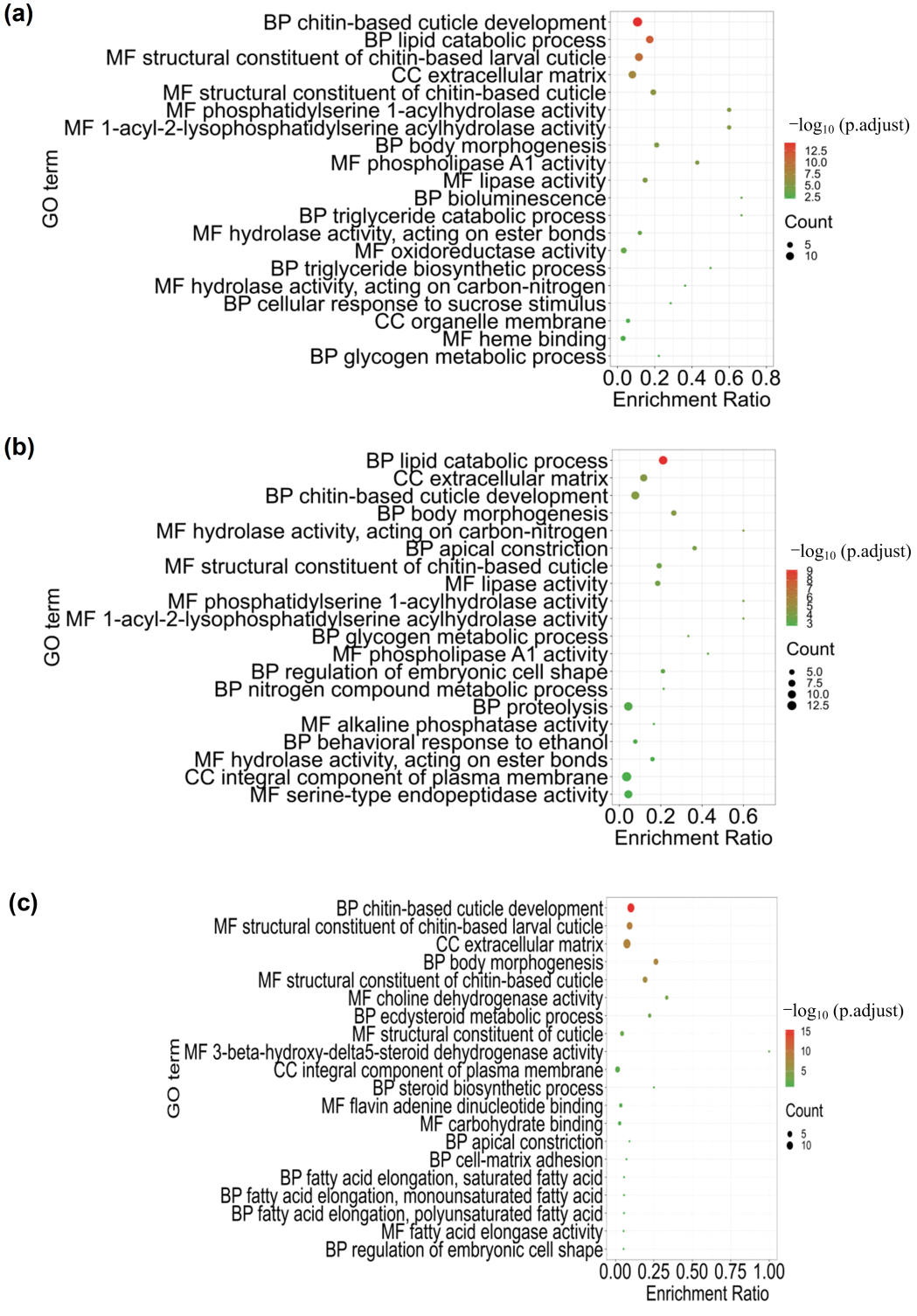
### 3.5 Verification of DEGs in Drosophila larvae and adults

According to the RNA-seq results, we selected 8 target genes for follow-up studies. The proteins encoded by *Apl*4, *CG*10814, *CG*11842, *CG*14089, *Prx*2540-1 and *CG*33012 are enzymes that perform different biological

functions[27], while the role of *CG*42815 and *CG*32071 is not yet known.

There are notable differences in gene expression under various nutrient conditions. Food containing sucrose strongly increases the mRNA level of *Apl*4, *CG*10814, *CG*42815 and *CG*32071. In contrast, threonine significantly up-regulates the mRNA level of *CG*11842, *CG*14089, *Prx*2540-1 (Figure 7(a)). Comparison between RT-qPCR and RNA-seq results (Figure 7(b)) showed that the trend of change is largely similar.

As females are more sensitive to nutrient consumption, we further tested the candidate gene expressions in adult females. As*CG*42815 is highly expressed in embryos and larvae, but lowly in adults[28]. *CG*32071 is also a salivary gland specific



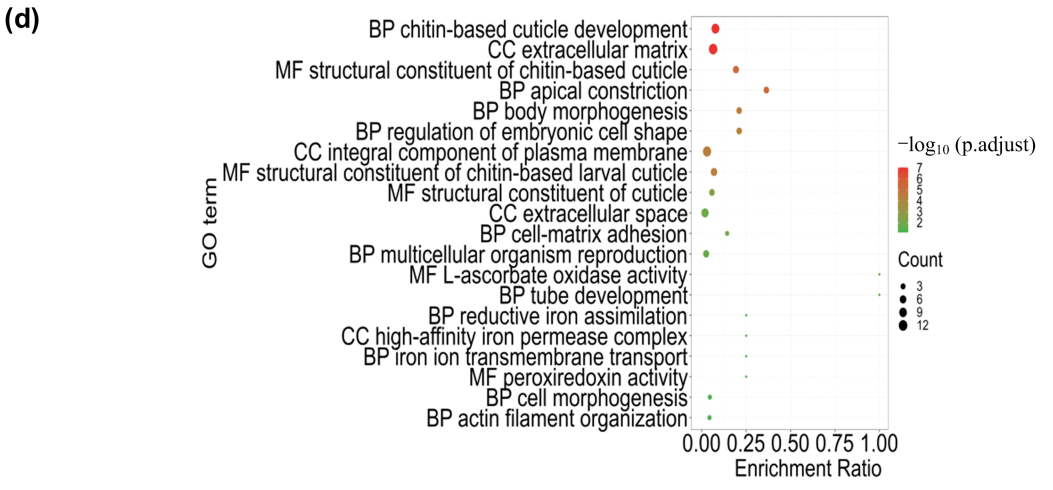



**Figure 6.** Bubble plot of GO enrichment. (a) Sugar vs Starvation. (b) Thr-Sugar vs Thr. (c) Thr-Sugar vs Sugar. (d) Thr vs Starvation. The top 20 terms with the smallest *p*-values adjusted for multiple comparison were presented. All genes with significant changes, including both up and down-regulated genes, were used for DEG analysis.

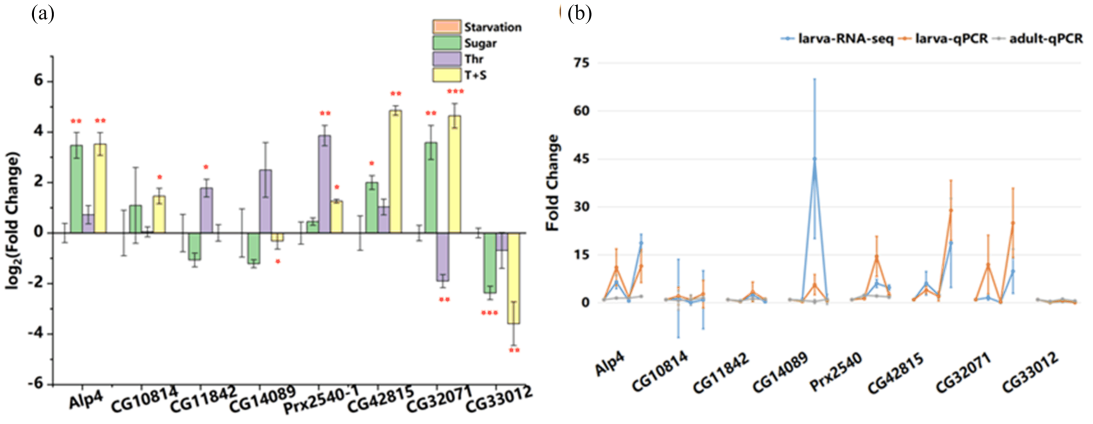



**Figure 7.** Gene expression between different dietary groups. (a) Fold change (in $\log_2$ scale) of selected genes quantified by RT-qPCR. Significance is calculated comparing different diets with starvation condition and *p*-values adjusted for multiple comparisons were presented. (b) Comparison of gene expression trends between larval RNA-seq, larval RT-qPCR, and adult RT-qPCR. For each gene term, the dot from left to right represents Starvation, Sugar, Thr, and Thr-Sugar. More than 3 biologically replicates were conducted for each condition.

gene mainly expressed at larval stage[28]. Therefore, neither of them was detected at the adult stage. Comparing the expression levels of the detected candidate genes between larvae and adults (Figure 7 (b)), we found that the changes of these genes are quite different (except for *CG*11842 and *CG*33012), suggesting that larval and adult fly may sense nutrition through distinctive machinery.

## 4 Conclusions

In this work, we studied the dietary preferences and food uptake of *Drosophila melanogaster* and identified amino acids preferred and consumed differently by male and female flies. Threonine is found to be a unique amino acid that promote food consumption in both presence and absence of sugar. Further locomotor ability assay indicates that threonine uptake significantly affected adult female motility. To identify the effector of threonine consumption, we then fed the third instar larvae with four different diets and profiled the transcriptomes of different groups. GO enrichment and KEGG pathway analysis of DEGs revealed that threonine influences steroid hormone and redox signaling pathways. From the candidate DEGs, we selected 8 significantly changed genes, validated, and compared their expressions in both larvae and adults under different dietary conditions by RT-qPCR. Our study explored the association between specific amino acids and animal nutrition perception and metabolic regulation, as well as provides a basis to further identify

the molecular mechanism by expression profiling.

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## Conflict of interest

The authors declare no conflict of interest.

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**XU Tong** is currently pursuing her master's degree under supervision of Prof. HE Li at University of Science and Technology of China. Her research interests include amino acids on the metabolism of Drosophila melanogaster.

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# 特定氨基酸对黑腹果蝇代谢的影响

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**摘要**: 为研究特殊氨基酸在动物体内的生物感知和生理作用,测定了果蝇对 20 种氨基酸的饮食偏好性及进食量,并检测了不同氨基酸对果蝇运动水平的影响. 研究发现,不同性别的果蝇对于不同种类的氨基酸具有独特的进食偏好,而苏氨酸可以显著影响果蝇的运动能力. 进一步以苏氨酸为主要研究对象,对果蝇三龄幼虫给予饥饿、苏氨酸、蔗糖以及苏氨酸混合蔗糖的饮食处理,通过转录组高通量测序,分析组间基因差异. 通过 Gene Ontology 和 Kyoto Encyclopedia of Genes and Genomes 富集分析发现,苏氨酸进食特异地对于果蝇的固醇类激素和氧化还原信号产生影响. 进一步利用实时荧光定量 PCR,对筛选获得的 8 个差异表达基因进行了验证,并通过对比成虫和幼虫发现不同发育阶段对于苏氨酸的响应可能存在较大差异. 本工作为进一步深入研究特定氨基酸在动物中的感知和代谢调节提供了现象基础,并为发现其具体分子机制提供了基因表达的线索.

**关键词**: 氨基酸代谢;黑腹果蝇;进食偏好;苏氨酸;转录谱分析

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# 一种新型的标准二次规划方法实现固定射野调强放疗的角度优化

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**摘要**: 射束角度优化极大程度上决定了固定野调强放疗的效果,但其一般被认为是一个非凸的 NP 难问题. 本文将该问题转化为一个标准的二次规划问题进行高效求解. 每个射野的最大出光强度被选作稀疏化指标,通过重赋权的 L1 最小化方法结合线性约束条件,实现射束角度稀疏化. 该方案的有效性在一个数字模体和两个临床案例上进行了验证. 最终得出结论:新的凸优化方法可以实现高效准确的放疗射束角度稀疏化,在治疗中更好地保护了危及器官.

**关键词**: 射束角度优化;调强放疗;标准二次规划