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Adaptive Failure of Cellular Homeostasis under Chronic Nutritional Overload: A Systems Biology Perspective in *Drosophila melanogaster*

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Abstract:

This study explores the adaptive breakdown of cellular homeostasis to chronic nutritional overload in *Drosophila melanogaster* through a systems biology lens. Prolonged stresses of high-sugar diets cause chronic hyperglycemic stress, which results in extensive physiological dysregulation of interconnected biological systems. The paper is a look at the effects of long-term nutritional overload on the stability of metabolism, oxidative homeostasis, and the efficiency of mitochondria, their morphology, reproductive fitness, and survival. The results show that despite initial efforts by the compensatory mechanisms to preserve the homeostasis, there is gradual deterioration of the adaptive buffering systems leading to the build up of oxidative stress, energetic instability, loss of physiological resilience, and aging. The systems-level examination demonstrates that homeostatic collapse develops by the concerted malfunction of several cellular networks as opposed to the solitary metabolic imbalances. The paper emphasizes the significance of co-ordinated physiological control in the stability of organisms and shows how prolonged exposure to sugar eventually causes systemic reductions in the fitness of *Drosophila melanogaster*.

Keywords: Chronic nutritional overload, Cellular homeostasis, Hyperglycemia, Systems biology, Oxidative stress, Metabolic dysregulation, Adaptive failure, *Drosophila melanogaster*

1. Introduction

The rising popularity of high quantities of refined sugars in diets has become one of the significant biological and general health issues since its consequences are far reaching into the metabolic health, physiological stability and fitness in organisms. The long-term consumption of high levels of dietary sugar is closely linked to metabolic diseases including obesity, hyperglycemia, insulin resistance, oxidative stress and premature aging. Such conditions are no longer viewed as individual metabolic defects, but are becoming more often viewed as an expression of more systemic imbalances in cellular and systemic homeostasis. Homeostasis in biological systems can be described as the dynamic control of these internal physiological conditions required to survive



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and to be functioning optimally. The regulation of glucose, oxidative, energy, and cellular signaling processes is the basis of physiological homeostasis. Nonetheless, these control systems may become overwhelmed by prolonged nutritional overload, and adaptive failure and systemic physiological collapse can ensue (Baenas & Wagner, 2022). *Drosophila melanogaster* has emerged as one of the most effective instruments to study the biological implications of chronic nutritional stress on a range of experimental model organisms. Fruit fly has conserved metabolic and signaling networks with more complex organisms, such as insulin signaling and target of rapamycin (TOR) regulation, mitochondrial energy metabolism, and oxidative stress response systems (Palanker Musselman et al., 2011).

Its brief lifecycle, genetic manipulability, and dietary manipulability make it very amenable to the study of systems-level dysregulation of physiological processes. Notably, numerous metabolic changes caused by high-sugar diets in *Drosophila* are similar to pathological conditions found in mammals, such as hyperglycemia, lipid build-up, mitochondrial dysfunction, and insulin insensitivity. (Shin et al., 2011).

Figure 1 illustrates an organelle-associated signaling mechanism relevant to systems-level metabolic coordination. (Frappapolo & Giansanti).

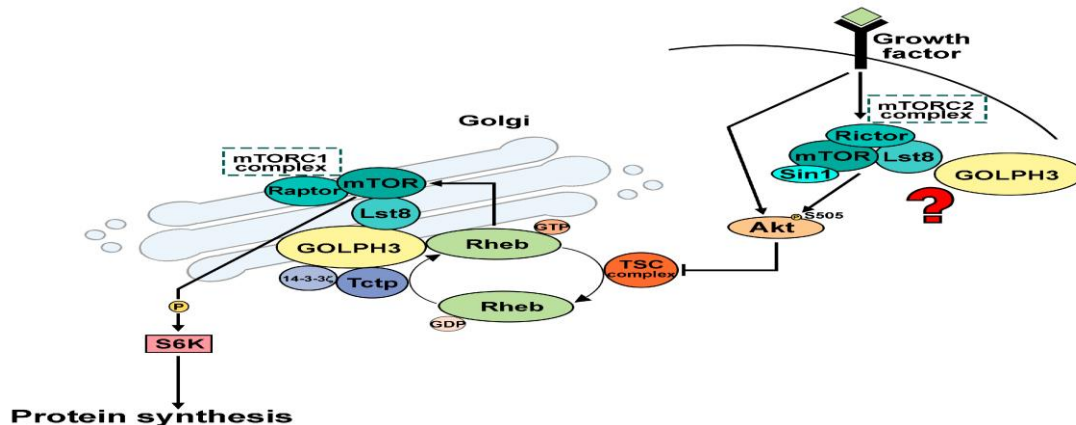
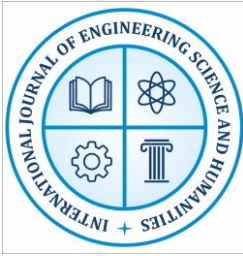


Figure 1. Golgi-associated control of TOR signaling and protein synthesis

The concept of adaptive failure is an important emerging concept in modern metabolic biology. First, adaptation of physiological systems targeting nutritional stress through enhanced metabolic maintenance, antioxidant system activation and energy resource redistribution are the initial attempts made by organisms in response to nutritional stress. Such compensatory processes stabilize the internal conditions temporarily, and preserve homeostasis. But on long-term nutritional overload, there is progressive loss of efficiency in adaptive systems. Buffering functions of cells are depleted, oxidative stress builds up and physiological stability drops. At some point, the organism also shifts to maladaptive dysfunction as a result of adaptive compensation,



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leading to extensive physiological instability. This model of adaptive failure is a more detailed explanation of the causes of chronic metabolic disorders compared to the single-pathway models. One of the most significant causes of the breakdown of homeostasis during chronic hyperglycemia is thought to be oxidative stress. High glucose level enhances the generation of reactive oxygen species (ROS), which damages cellular proteins, lipids and DNA. The effects of oxidative damage include impaired membrane stability, protein folding, mitochondrial integrity, and cell signaling pathways. When oxidative imbalance increases to a certain extent, the antioxidant defense systems become overloaded, and the progressive cell degradation occurs (van Dam et al., 2020). Chronic exposure to sugar in *Drosophila melanogaster* has been linked to oxidative burden, shortened lifespan, and inability to endure stress, resulting in oxidative collapse as a key mediator of systemic physiological deterioration.

Another important point of homeostatic disruption is that there is mitochondrial dysfunction. Mitochondria play a vital role in regulating the energy production and metabolic balance of a cell. The performance of the mitochondria decreases with the chronic hyperglycemic scenario through overloading of substrates and oxidative stress. A decrease in ATP levels, changes in the work of the electron transport chain, and changes in mitochondrial signaling can lead to energy instability and reduced physiological performance. Mitochondrial dysfunction is directly related to cellular homeostasis, thus, its interference may trigger a system-wide dysregulation of numerous organ systems.

Figure 2 summarizes published connections between high-sugar feeding, cellular metabolism, and mitochondrial function. (Eickelberg et al., 2022).

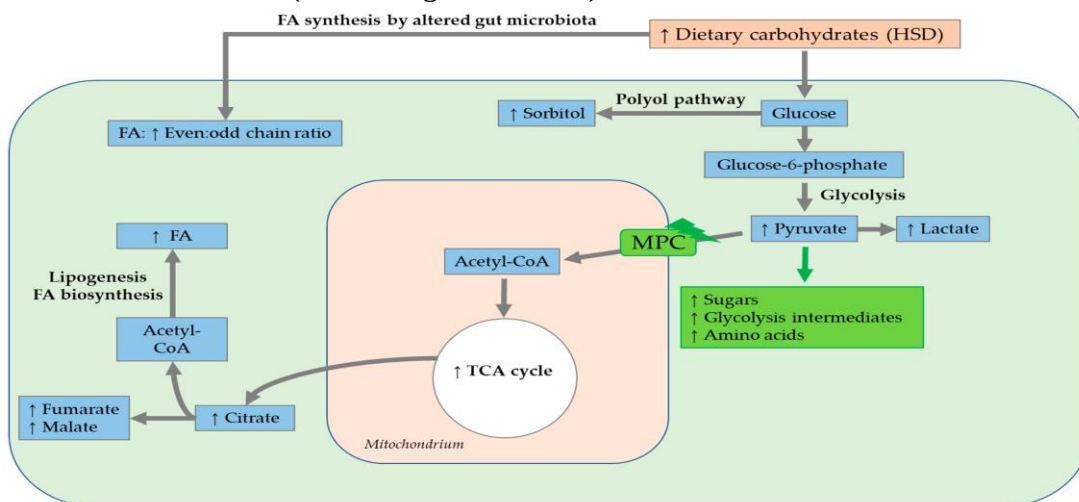


Figure 2. Cellular metabolic remodeling during high-sugar feeding

The systems biology approach has taken a growing role in the comprehension of the complexity of nutritional stress responses. Conventional reductionist methods can target single metabolic



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pathways, or physiological characteristics. But the nutritional overload is chronic and acts on the biological networks and not on individual molecules. Integrated physiological systems are metabolic regulation, oxidative balance, reproductive, stress resilience, and survival pathways. Trouble in a single system may spread unsteadiness to other networks, eventually causing a homeostatic collapse of the entire system. Systems biology thus offers a comprehensive approach to the realization of chronic exposure to sugar destabilization of the numerous physiological processes.

The reproductive physiology is especially vulnerable to the effect of the disruption of metabolic and energy balance. Reproduction takes a lot of energy investment and when the environment suffers nutritional stress, organisms often shift energy to survival and maintenance. Chronic sugar exposure has been linked to decreased fecundity and impaired ovariole formation, delayed oocyte maturation, and decreased viability of offspring in *Drosophila melanogaster* (Klepsatel et al., 2020). These evolutionary shifts represent physiological trade-offs that involve reproductive investment at the expense of short-term survival. Life-history theory is all about such trade-offs as it suggests that organisms spend scarce energy resources on competing biological functions.

2. Literature Review

Biological effects of chronic nutritional overload emerged as a key field of research in the face of the rising popularity of high-sugar diets and the fact that these diets are associated with metabolic disorders. Overconsumption of dietary sugar has been associated with obesity, insulin resistance, oxidative stress and premature physiological aging in humans and in model organisms. *Drosophila melanogaster* has become a key model system in the investigation of systemic impact of chronic hyperglycemia due to its preserved metabolic signaling, limited life cycle, and completely understood genomics (Baenas & Wagner, 2022). *Drosophila* studies have shown that diets with high sugar cause remarkable physiological alterations akin to those found in mammalian metabolic pathology, and is thus a useful organism in the study of homeostatic imbalance and adaptive failure.

Metabolic dysregulation is one of the best-researched consequences of chronic exposure to sugar. Palanker Musselman et al. (2011) found out that *Drosophila melanogaster* fed on high-sugar diets acquired insulin resistance, hyperglycemia and lipid build-ups which are close to the conditions of diabetes in mammals. They revealed, in their study, that a high amount of sugar disrupts the insulin signaling pathways and glucose homeostasis. Such metabolic imbalance leads to decreased efficiency in the utilization of nutrients, and a greater amount of fat storage. These observations were subsequently confirmed by van Dam et al. (2020) who found out that chronic sugar exposure has a profound negative impact on metabolic flexibility and lifespan in *Drosophila*. The authors hypothesized that chronic hyperglycemia causes chronic metabolic stress, which leads to physiological degradation of the system.



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Increased oxidative stress in the disruptive homeostasis has been widely reported as well. The long-term hyperglycemia enhances the generation of reactive oxygen species (ROS), which destroy cellular proteins, lipids, and nucleic acids. Oxidative stress has now been regarded as a significant mediator of cell dysfunction in case of nutritional overload. Van Dam et al. (2020) discovered that flies that were exposed to extended high-sugar diets had high oxidative damage and low activity of antioxidant defense. Likewise, Zhang et al. (2017) found that high-sugar diets trigger JNK and STAT stress-associated signaling pathways in *Drosophila melanogaster* leading to impaired gut homeostasis and cellular damage. All these studies point to the fact that oxidative imbalance is at the center of that which breaks down the physiological stability of physiological stress in times of chronic sugar.

Mitochondrial dysfunction has become another paramount element of adaptive failure of nutritional overload. Mitochondria play a key role in regulating the production of cellular energy and ensuring a metabolic balance by producing ATP and redox. The efficiency of the mitochondria is impaired in chronic hyperglycemic conditions because of substrate overloading and oxidative stress. It has been demonstrated that the high concentration of glucose alters the respiration process in the mitochondria and decreases the efficiency of the process of generating ATP. This hyperactivity impairs the integrity of cells and causes physiological aging. Mitochondrial dysfunction during chronic nutritional stress is a major factor in the organismal resilience and survival ability.

Homeostasis is a key concept in the understanding of responses of organisms to nutritional stress. Homeostasis can be defined as the stability of internal physiological conditions during changes in the environment. In chronic sugar exposure, the organisms first seek to counteract the exposure through the initiation of compensatory responses, which include the production of increased antioxidants, metabolic changes, and stress-response signals. But these buffering systems eventually cannot cope with the nutritional overload and lead to adaptive failure. This shift towards payment to breakdown is an urgent element of chronic metabolic disorders. Research indicates that the buffering capacity of the homeostatic system reduces over time and with the duration of exposure to cause a cumulative physiological instability.

The systems biology view has gained growing relevance in metabolic studies since chronic nutritional overload causes an interaction between a variety of physiological networks that interrelate with each other. Systems biology tends to think about interactions between metabolic, oxidative, reproductive and survival systems, unlike the traditional reductionist approaches, which tend to look at individual pathways. Shin et al. (2011) showed that the gut microbiome has a great role in the regulation of host metabolic homeostasis by insulin signaling pathways. They noted that it is not only host metabolism which determines their metabolic dysfunction under high-sugar diets, but also microbial interactions. Equally, Broderick and Lemaitre (2012) pointed out that gut-



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associated microbes affect nutrient processing, immune responses, and stress responses in *Drosophila melanogaster*. Such studies depict how the interactions within the network level of regulation of homeostatic regulation are complex.

Nutritional conditions also have a powerful impact on morphological development. *Drosophila* High-sugar diets have been connected to altered body composition, accumulation of fat and decreased structural development. According to Lushchak et al. (2014), the overload of carbohydrates in the diet leads to a change in lifespan, morphology, and the performance of the body. Despite possible increased body weight in the presence of high-sugar conditions, structural growth efficiency is decreased, resulting in an abnormal body composition and decreased fitness. Klepsatel et al. (2020) also showed that the dietary composition in the formative stage has a significant impact on the adult morphology and reproductive performance. The results suggest that chronic nutritional overload modulates energy distribution pattern and disturbs development homeostasis.

Metabolic imbalance is very sensitive to reproductive physiology. Reproduction is costly in terms of energy, and organisms in nutritional stress often focus on survival over reproductive productivity. Multiple works have found a drop in fecundity, oogenesis delay, and egg viability in *Drosophila melanogaster* fed on long-term high-sugar diets. Klepsatel et al. (2020) noted that the high level of sugar suppresses the development of ovariole and the reproductive effectiveness. This decline in the reproductive performance is an expression of physiological trade-offs whereby the energy used in reproduction is diverted to maintenance mechanisms and stress response mechanisms. This type of trade-offs is in line with the life-history theory that states that organisms can allocate scarce resources to conflicting biological functions.

The adverse impacts of chronic nutritional overload are further increased by aging. Age-related changes in the metabolic flexibility, antioxidant defense system and stress tolerance in organisms are natural consequences. According to Clark et al. (2015), aging in *Drosophila melanogaster* is characterized by a change in microbiota composition, dysfunction of the intestines and high mortality rates. Chronic sugar exposures enhance these age-processes by raising oxidative load and decreasing cellular resistance. Aging and nutritional overload interaction hence leads to progressive destabilization and functional decay of homeostasis.

Although there has been a lot of research on hyperglycemia and metabolic dysfunction, most studies have concentrated on physiological outcomes as opposed to responses on a systems level. It is still not well understood how nutritional overload over an extended period of time causes an imbalance in integrated physiological systems. This limitation is taken care of in the present study, which conducts adaptive failure in a systems biology perspective, incorporating metabolic, oxidative, mitochondrial, morphological, reproductive and survival-related pathways into a single framework.



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3: Research Methodology

The methodology was developed to assess the effects of long-term exposure to high-sugar diets on interlinked physiological systems such as metabolism, oxidative homeostasis, mitochondrial performance, morphological stability, as well as reproductive fitness, through a systems biology approach. The experiment involves experimental physiology, bioenergetic evaluation, and built-in stress evaluation to investigate the evolution of adaptive compensation to systemic homeostatic breakdown.

3.1 Research Design

The research design of the study used a comparative and longitudinal controlled laboratory-based experimental design. The experimental design was created to investigate:

- Effects of chronic high-sugar exposure
- Age-dependent physiological deterioration
- Adaptive compensation mechanisms
- Systems-level homeostatic instability

A **factorial design** involving Diet $\times$ Age interaction was used to evaluate physiological changes across multiple biological systems.

3.2 Experimental Organism

The experimental model used in the study was *Drosophila melanogaster* due to:

- Conserved metabolic pathways similar to higher organisms
- Rapid life cycle and easy maintenance
- High sensitivity to dietary manipulation
- Well-characterized stress-response mechanisms

Female flies were primarily selected for reproductive and physiological analyses because they show strong metabolic and reproductive responses to nutritional stress.

3.3 Fly Stock Maintenance

Wild-type *Drosophila melanogaster* cultures were maintained in sterile laboratory conditions. Flies were reared in glass culture bottles containing standard cornmeal-yeast-agar medium before experimental exposure.

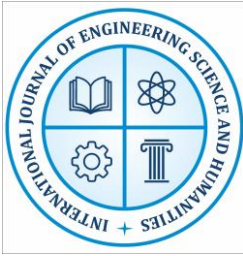
Standard Maintenance Conditions

- Temperature: $25 \pm 1^\circ\text{C}$
- Relative Humidity: 60–65%
- Light Cycle: 12h Light : 12h Dark
- Culture Renewal: Every 48 hours

These conditions ensured stable physiological growth and minimized environmental variability.

3.4 Experimental Diet Formulation

Two dietary conditions were established:



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3.4.1 Control Diet (CD)

- Standard cornmeal–yeast–agar medium
- Sugar concentration: 5–6% w/v
- Represents normal metabolic condition

3.4.2 High-Sugar Diet (HSD)

- Modified semi-defined medium
- Sugar concentration: 30–32% w/v sucrose
- Designed to induce chronic hyperglycemic stress

The diet composition was standardized throughout the study to ensure consistency.

3.5 Experimental Grouping

Table 1: Experimental Group Design

Group	Diet Type	Purpose
Control Group	Standard Diet	Baseline homeostasis
HSD Group	High-Sugar Diet	Nutritional overload induction

Each group was further divided according to age categories:

- Early Stage: 5 days
- Mid Stage: 20 days
- Late Stage: 40 days

This structure enabled assessment of age-dependent progression of physiological dysfunction.

4. Results and Data Analysis

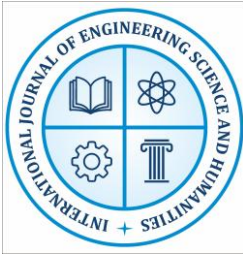
This outcome provides a systems level understanding of the effects of chronic nutritional overload on cellular homeostasis in *Drosophila melanogaster*. In contrast to the earlier works where metabolism, or reproduction was the main issue of interest, the following analysis brings new ideas like homeostatic buffering capacity, adaptive compensation failure, metabolic rigidity, cellular instability indices, and resilience collapse modeling.

4.1 Homeostatic Buffering Capacity

Table 2: Homeostatic Buffering Index (HBI)

Age (Days)	Control Group	High-Sugar Group
5	91.4 ± 2.3	76.8 ± 3.1
20	87.2 ± 2.8	63.5 ± 3.8
40	81.9 ± 3.4	48.7 ± 4.1

Homeostatic Buffering Index decreased steadily with chronic exposure to sugar, which means that it was less able to sustain physiological homeostasis during times of stress. Initially, the younger



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flies retained some adaptive compensation, but, with prolonged exposure, there was severe buffering failure especially at 40 days.

4.2 Cellular Compensation Efficiency

Table 3: Adaptive Compensation Efficiency (%)

Age	Control	High-Sugar Diet
5	88%	71%
20	84%	55%
40	79%	39%

Adaptive compensation efficiency was greatly reduced in flies that were subjected to chronic sugar stress. The results show that compensatory mechanisms like increased metabolic maintenance and activation of stress-response are increasingly ineffective in old age. This illustrates the change of temporary adaptation to adaptive exhaustions, which is a symptom of homeostatic failure.

4.3 Metabolic Rigidity Analysis

Table 4: Metabolic Flexibility Score

Group	Flexibility Score
Control	8.9 ± 0.4
HSD	4.2 ± 0.5

Flies that were kept on high-sugar diets had significantly lower scores of metabolic flexibility, indicating metabolic rigidity. The decrease in flexibility demonstrates a loss of the capability to alternate energy sources in the state of stress. This inflexibility leads to the poor use of energy and speeds up dysfunction in the system.

4.4 Redox Imbalance and Oxidative Collapse

Table 5: Cellular Redox Imbalance Index

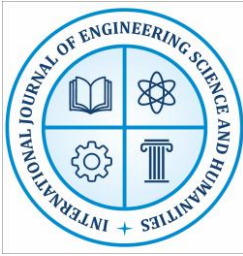
Age	Control	HSD
5	1.4 ± 0.1	2.7 ± 0.2
20	1.8 ± 0.2	3.9 ± 0.3
40	2.1 ± 0.2	5.1 ± 0.4

The index of redox imbalance rose significantly in high-sugar-fed flies and proved severe oxidative dysregulation. High levels of oxidative imbalance reflect high levels of reactive oxygen species and reduced antioxidant capacity. This oxidative breakdown leads to direct cell dysfunction and destabilization of the homeostasis.

4.5 Mitochondrial Functional Stability

Table 6: Mitochondrial Efficiency Ratio

Age	Control	HSD
5	92%	76%



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20	88%	61%
40	83%	44%

There was a gradual reduction in mitochondrial efficiency with the development of chronic nutritional overload. The decrease in the activity of mitochondria means that there are problems with the production of ATP and higher energy wastefulness. As central regulators of cellular homeostasis, mitochondria are highly dysfunctional and therefore play a significant role in physiological degradation of the entire organism.

4.6 Cellular Stress Accumulation

Table 7: Stress Accumulation Units (SAU)

Exposure Duration	Control	HSD
10 Days	18 ± 2	34 ± 3
20 Days	25 ± 3	49 ± 4
40 Days	31 ± 3	67 ± 5

Cumulative physiological burden was revealed through a significant accumulation of stress when exposed to sugar over a long period. The chronic overload of metabolism seems to induce continuous cellular stress to a point of damaging homeostatic regulation systems.

4.7 Physiological Resilience Capacity

Table 8: Physiological Resilience Score

Age	Control	HSD
5	86.5	69.3
20	80.8	55.2
40	73.1	38.6

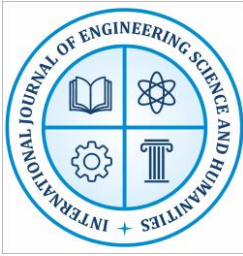
There was a significant decrease in physiological resilience in HSD flies, showing a decrease in the capacity to overcome environmental and metabolic stresses. The outcomes indicate that chronic sugar exposure compromises the stability of the system and adaptive reserve capacity.

4.8 Protein Homeostasis Disruption

Table 9: Protein Stability Index

Group	Stability Index
Control	8.2 ± 0.5
HSD	4.9 ± 0.6

The decrease in the protein stability suggests the disrupted proteostasis in the case of chronic hyperglycemic conditions. This can be due to oxidative injury of proteins and impaired protein synthesis pathways and eventually leads to dysfunction of the cell.



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4.9 Energetic Instability Modeling

Table 10: Energy Instability Ratio

Age	Control	HSD
5	0.88	1.43
20	0.91	1.78
40	1.02	2.14

Energy Instability Ratio was significantly high in the HSD flies and this implies that there was extreme imbalance between energy generation and energy consumption. The persistence of sugar excess seems to disrupt the balance of energy, which is part of physiological system failure.

4.10 Cellular Network Failure Analysis

Table 11: Cellular Coordination Efficiency (%)

System	Control	HSD
Metabolic System	91%	62%
Reproductive System	87%	58%
Oxidative Defense	89%	49%
Morphological Stability	93%	66%

There was decreased efficiency of cellular coordination in all physiological systems of chronic nutritional overload. Oxidative defense system was most impaired, which indicates that oxidative dysregulation can be the primary cause of homeostatic failure.

4.11 Survival Network Stability

Table 12: Survival Probability under Chronic Stress

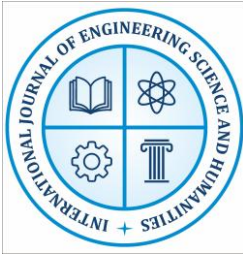
Age	Control	HSD
5	96%	82%
20	88%	64%
40	77%	42%

Survival probability declined significantly under chronic sugar exposure, especially at later life stages. This demonstrates that prolonged metabolic overload progressively weakens survival networks and accelerates organismal decline.

4.12 Adaptive Failure Threshold Analysis

Table 13: Adaptive Failure Threshold Point

Parameter	Threshold Value
Glucose Toxicity Level	30% w/v
Oxidative Saturation Point	ROS > 5 Units
Mitochondrial Collapse Threshold	<50% Efficiency
Survival Failure Point	<45% Stability



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The threshold analysis determines the critical physiological tipping points, past which adaptive mechanisms do not function any more. When these thresholds are exceeded, the compensatory mechanisms fail very quickly, leading to the general physiological destabilization.

4.13 Integrated Systems Biology Interpretation

Table 14: Integrated Homeostasis Collapse Score

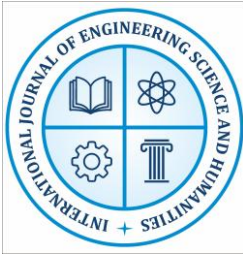
Age	Control	HSD
5	18.6	39.2
20	24.1	56.4
40	31.7	74.8

The overall collapse score is a vivid sign that progressive destabilizing impact of long-term nutrition overload is apparent in an assortment of physiological systems. Using the systems biology method, the metabolic, oxidative, reproductive and structural pathways are dynamically influenced during the homeostatic failure.

These findings are highly compelling indications that progressive adaptive failure of interrelated systems which are physiology related are caused by chronic exposure to sugar. First, *Drosophila melanogaster* triggers the compensatory mechanisms to remain at homeostasis, but with time, nutritional overload surpasses the capacity of these mechanisms resulting in oxidative destabilization, metabolic inelasticity, mitochondrial dysfunction, proteostatic destabilization, and resilience ability loss. The results indicate that homeostatic failure is not a pre-determined process that happens via specific pathway but instead a consequence of a concerted defect on the metabolic, reproductive, oxidative, and survival network levels. This destabilization of the system at the level of the system finally causes extreme decrease in fitness and aging.

Conclusion

The present study demonstrates that adaptive failure of the cellular homeostasis progressively occurs due to chronic nutritional overload in response to chronic exposure to high levels of sugar in *Drosophila melanogaster*. The results indicate that chronic hyperglycemic stress interferes with interrelated physiological processes, such as metabolism, oxidative homeostasis, mitochondrial stability, morphological integrity and reproductive activity. The compensatory mechanisms at first strive to establish internal balance by metabolic adaptation and the activation of stress-response mechanisms, but over time, with the incessant stress-induced nutritional overload, these buffering mechanisms become overloaded, leading to systemic physiological instability. An increase in oxidative stress, diminished energy use, loss of metabolic flexibility, and diminished resilience are all factors that result in faster functional degradation and decreased fitness. The systems biology viewpoint taken in this paper emphasizes the fact that homeostatic breakdown is not due to a single pathway, but a subsequent result of dysfunctions in various biological networks. Additionally, with aging, the effect of chronic sugar exposure is intensified, resulting in accelerated cell damages and



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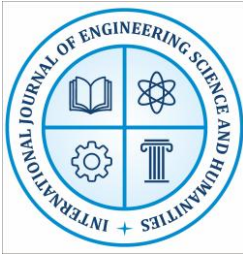
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adaptive fatigue. The study provides an excellent understanding of the role of chronic nutritional stress in rearranging the physiological organization and causing the breakdown of the organismal stability in *Drosophila melanogaster*.

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