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Royal Jelly Supplementation Enhances Post-Exhaustive Exercise Energy Metabolism

Arı Sütü Takviyesi Yoğun Egzersiz Sonrası Enerji Metabolizmasını İyileştirir

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ABSTRACT

Introduction: Lactate accumulation, free radical increase and changes in the activity of regulatory enzymes in energy metabolism that occur after acute exhaustion exercise disrupt the muscle adaptation mechanism and lead to muscle damage. Royal jelly, which is considered a superfood with its cell regeneration and therapeutic effects, can compensate for the effects that occur after exercise.
Objective: In this study, the effects of royal jelly supplementation were investigated in Balb-c type mice in which an acute exhaustion exercise model was created.
Methods: Mice were randomly divided into four groups: control, royal jelly, acute exhaustion exercise, acute exhaustion exercise + royal jelly. In all groups, the levels of mitochondrial biogenesis markers Ppargc1a and TFAM, which regulate muscle adaptation, and the levels of PDHa and Slc16a1, which are effective in aerobic and anaerobic regulation, were analyzed by ELISA method.
Results: PDHa and Slc16a1 levels were statistically significant between groups (p=0.024, p=0.029, respectively), but Ppargc1a and TFAM levels were not significant between groups (p=0.087, p=0.082, respectively). It was found that PDHa, Slc16a1, Ppargc1a and TFAM levels increased in the group receiving royal jelly supplementation with acute exhaustion exercise compared to the group not receiving supplementation.
Conclusions: These findings highlight the effective potential of royal jelly in developing/improving aerobic and anaerobic respiratory pathways and in the muscle adaptation process against the impaired muscle adaptation mechanism caused by acute exhausting exercise. Based on these promising results, further research is required to explore new knowledge in exercise physiology and sports sciences.

Keyswords: Acute Exhaustion Exercise, Royal Jelly, Muscle Adaptation, Energy Metabolism.

ÖZET

Giriş: Akut tükenme egzersizi sonrası ortaya çıkan laktat birikimi, serbest radikal artışı ve enerji metabolizmasındaki düzenleyici enzimlerin aktivitesindeki değişiklikler kas adaptasyon mekanizmasını bozmakta ve kas hasarına yol açmaktadır. Hücre yenilenmesi ve terapötik etkileri ile süper gıda olarak kabul edilen arı sütü egzersiz sonrası oluşan etkileri kompanse edebilir.
Amaç: Bu çalışmada, akut tükenme egzersiz modeli oluşturulmuş Balb-c türü farelerde arı sütü takviyesinin etkileri araştırıldı.
Yöntem: Kontrol, arı sütü, akut tükenme egzersizi, akut tükenme egzersizi + arı sütü grubundan oluşan fareler rastgele dört gruba ayrıldı. Tüm gruplarda, kas adaptasyonunu düzenleyen mitokondriyal biyogenez belirteçleri Ppargc1a ve TFAM düzeyleri, aerobik ve anaerobik düzenlemede etkili olan PDHa ve Slc16a1 düzeyleri ELISA yöntemiyle analiz edildi.
Bulgular: PDHa ve Slc16a1 düzeyleri gruplar arasında istatistiksel olarak anlamlıydı (sırasıyla, p=0,024, p=0,029) ancak Ppargc1a ve TFAM düzeyleri gruplar arasında anlamlı değildi (sırasıyla, p=0,087, p=0,082). Akut tükenme egzersizi ile arı sütü takviyesi alan grupta PDHa, Slc16a1, Ppargc1a ve TFAM düzeylerinin takviye almayan gruba göre arttığı bulundu.
Sonuç: Bu bulgular akut tükenme egzersizi kaynaklı bozulmuş kas adaptasyon mekanizmasına karşı arı sütünün aerobik ve anaerobik solunum yolunu geliştirmesi/iyileştirmesi ve kas adaptasyon sürecindeki etkili potansiyelini vurgulamaktadır. Bu ümit verici sonuçlara dayanarak egzersiz fizyoloji ve spor bilimlerindeki yeni bilgileri keşfetmek için daha fazla araştırma yapılması gerekmektedir.

Anahtar Kelimeler: Akut Tükenme Egzersizi, Arı Sütü, Kas Adaptasyonu, Enerji Metabolizması.

INTRODUCTION

Acute exhaustion exercise is defined as a temporary exhaustion state that occurs after intense exercise that exceeds physical capacity. This type of exercise causes rapid depletion of energy stores in the muscles, lactate accumulation, muscle fatigue and increased oxidative stress. Increased oxidative stress and free radical production in the body can lead to cellular damage, triggering inflammation and

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proteolytic processes in muscle tissue (1). In particular, microdamages occur in the muscles, triggering inflammatory responses and delaying muscle recovery. Acute depletion can also have temporary depressant effects on the immune system, increasing the risk of post-exercise infection (2). These effects may slow muscle recovery and healing.

Royal jelly, which has a rich composition of proteins, peptides, carbohydrates, fatty acids, organic acids and other bioactive compounds with high biological value, is considered a super food with functional and nutritional properties (3). It has been used for centuries in traditional Chinese medicine due to its anti-aging effects and positive effects on the immune system (4). The bioactive substances in royal jelly reduce oxidative stress and prevent cell damage, and are thus considered a potential treatment strategy in preventing many chronic diseases (3).

It is known that exercise increases fuel oxidation, mitochondrial ATP production and muscle contraction by improving muscle metabolism. These support muscle adaptation and improve muscle health. Chronic conditions such as obesity, diabetes, muscle diseases and aging are associated with a decrease in muscle function and cause these processes to progress (5,6) Considering these negative effects, understanding the molecular mechanisms of exercise and fuel metabolism is extremely critical and has significant potential (7). It has become important to identify molecular mechanisms and develop strategies that can antagonize possible adverse effects, especially in acute exhaustion exercise where muscle adaptations are impaired.

Previous studies have demonstrated that royal jelly can enhance endurance, improve mitochondrial function, and stimulate energy metabolism in animals (8). However, the potential effects of royal jelly in acute exhaustion exercise, where muscle adaptations are impaired, have not been investigated. Specific effects of mitochondrial biogenesis regulators such as Ppargc1 and TFAM, which are directly related to muscle adaptations, and metabolic enzymes such as PDHa and Slc16a1, which regulate the aerobic/anaerobic respiratory pathway, have not yet been sufficiently investigated. Royal jelly may contribute to the regulation and improvement of undesirable adaptations caused by acute exhaustion exercise by affecting the levels of these metabolic markers.

In this study, the effects of royal jelly supplementation were investigated in Balb-c mice with an acute exhaustion exercise model. These effects are discussed with the levels of mitochondrial biogenesis markers Ppargc1 and TFAM, which regulate muscle adaptation, and the levels of PDHa and Slc16a, which are effective in aerobic and anaerobic regulation.

METHOD

Animals

The study protocol was approved by the Local Ethics Committee on Animal Studies of Harran University (approval number 2024/003/09). Twenty-eight male Balb/c (8-10 weeks old) mice were supplied by Experimental Animals Application and Research Center of Harran University (Şanlıurfa, Türkiye). All animals were acclimatized for one week under standard conditions (room temperature 22 ± 2 °C and 12 h light/dark cycle). Water and standard food pellets were allowed ad libitum. All animals received human care according to the criteria outlined in the “Guide for the Care and Use of Laboratory Animals” published by the National Institutes of Health.

Experimental Procedures and Groups

The mice were randomized into four groups: control group, royal jelly (RJ) group, exercise group, and RJ+Exercise group. Royal jelly was administered to the experimental group of mice via gavage at a dose of 1 mg/g body weight for 14 days, in addition to their standard diet. The Exercise and RJ+Exercise group underwent a one-week familiarization period before starting the training intervention. During this period, animals exercised on a treadmill for 10 min at 10 m/min per session. Electric shock (0.5 mA) was also used to stimulate animals to run. Two weeks after the last familiarization session, they performed an acute exhaustive treadmill test. The test started for 5 min at 10 m/min and increased 2 m/min every 1 min. The acute exhaustive exercise protocol was implemented on a motorized treadmill at 32 m/min of speed until exhaustion. Despite all physical and electrical stimuli, the absence of any

activity or immobilization on the treadmill was considered as exhaustion and the running process was terminated. Immediately after euthanizing, muscle tissue (M. gastrocnemius) samples were collected from each group, which were stored at −80 °C. The muscle tissue samples was homogenized in ice-cold phosphate-buffered saline (gr tissue piece/10XPBS vol.). 1 mM PMSF protease inhibitor in PBS was used. The homogenates were centrifuged for 5 min. at 5000 g, and the supernatant obtained was stored at –80° C until the assays. The total protein concentration in the tissue was determined using the bicinchoninic acid assay method.

Measurement of Metabolic Analyses

The muscle tissue PDHa (Cat.No: EM1274), Slc16a1 (Cat.No: EM0793), Ppargc1a (Cat.No: EM0534), and TFAM (Cat.No: EM2518) levels were determined using a commercial ELISA kit following the manufacturer's instructions (FineTest, Wuhan Fine Biotech Co., Ltd., Hubei, China). The kits are based on the sandwich ELISA principle. The micro ELISA plate provided in those kits is pre-coated with an antibody specific to mouse PDHa (as with ELISA kits of Slc16a1, Ppargc1a, and TFAM). Muscle tissue homogenates (or Standards) are added to the micro ELISA plate wells and combined with the specific antibody. After incubation and washing process are added biotin-labeled antibody. After a second incubation and washing process are added HRP-Streptavidin Conjugate solution into each well. After incubation, artifacts are washed away. TMB substrate solution is added to each well and a final incubation is performed. The enzyme-substrate reaction is terminated by the addition of stop solution and the color turns yellow from blue. The optical density was measured with a microplate reader immediately (Varioskan LUX; Thermo Scientific) at a wavelength of 450 nm. The concentrations were calculated by comparing the OD of the samples with the standard curve. All results (except for TFAM) were expressed as ng/ mg protein, and TFAM level was expressed as pg/mg protein.

Statistical Analysis

SPSS statistical software version 24 (IBM Inc., Triangle Park, NC, USA) was used to perform all statistical analyses. The standard data distribution was tested with the Shapiro–Wilk test. Numerical variables were described using median and interquartile range values. The multi-group comparison of variables was conducted by Kruskal–Wallis test and pairwise comparisons were conducted by using Mann–Whitney U test with Bonferroni correction. For correlation, the Spearman correlation test was used. The relationship between the parameters was also shown with the heatmap matrix. A two-tailed p value < 0.05 was considered significant.

RESULTS

A total of 28 mice, 7 in each group, were included in the study. One of the mice in RJ group died during the study. The exercise protocol was completed as intended. Table 1 shows the comparison of PDHa, Slc16a1, Ppargc1a and TFAM muscle tissue levels among the control, Royal Jelly (RJ), Exercise, RJ+Exercise groups. According to Kruskal-Wallis analysis, PDHa and Slc16a1 levels was statistically significant between the groups (p=0.024, p=0.029, respectively) (Table 1, Figure 1). However, Ppargc1

Table 1. Muscle Tissue of PDHa, Slc16a1, Ppargc1a and TFAM Levels of The Subjects Within Groups

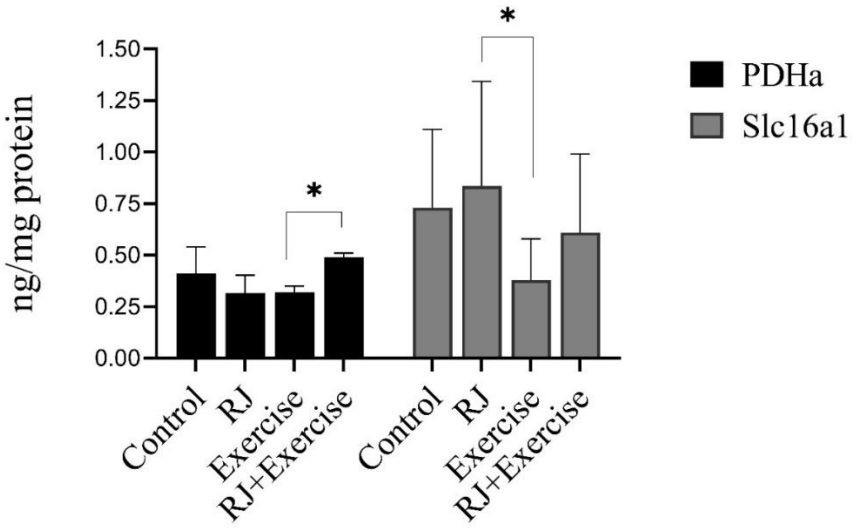
Parameters	Control n=7	RJ n=6	Exercise n=7	RJ+Exercise n=7	p*
PDHa, ng/mg protein	0.41 (0.22)	0.31 (0.11)	0.31 (0.14) α	0.49 (0.05)	0.024
Slc16a1, ng/mg protein	0.73 (0.46)	0.83 (0.76)	0.37 (0.26) β	0.60 (0.48)	0.029
Ppargc1a, ng/mg protein	0.82 (0.48)	0.49 (0.53)	0.34 (0.27)	0.53 (0.37)	0.087
TFAM, pg/mg protein	116.7 (61.37)	73.5 (77.3)	48.1 (39.9)	72.9 (60.6)	0.082

All The Data Were Expressed As The Median (Interquartile range), *Kruskal-Wallis Test, α: Exercise Group vs RJ+Excercise Group; β: Exercise Group vs RJ group. Abbreviations: RJ: Royal Jelly, PDHa: Pyruvate Dehydrogenase Alpha, Slc16a1: Monocarboxylate Transporter 1, Ppargc1a: Peroxisome Proliferator-Activated Receptor Gamma Coaktivator 1-Alpha, TFAM: Transcription Factor A, Mitochondrial.

Compared to the control group, PDHa activity was found to be lower in the RJ and exercise groups, while it was higher in the RJ+exercise group. In the intragroup comparison with Bonferroni correction, the difference between the RJ+exercise group and the exercise group was statistically significant (p=0.038). Although Slc16a1 levels varied between groups, the lowest Slc16a1 levels were in the

exercise group and the highest levels were in the RJ group. The difference between the exercise and RJ groups was statistically significant (p=0.041). Mitochondrial biogenesis parameters Ppargc1a and TFAM levels were found to decrease in the RJ, exercise and RJ+exercise groups compared to the control group. Ppargc1a and TFAM levels in the RJ+exercise group were higher than in the RJ and exercise groups, but were not statistically significant.

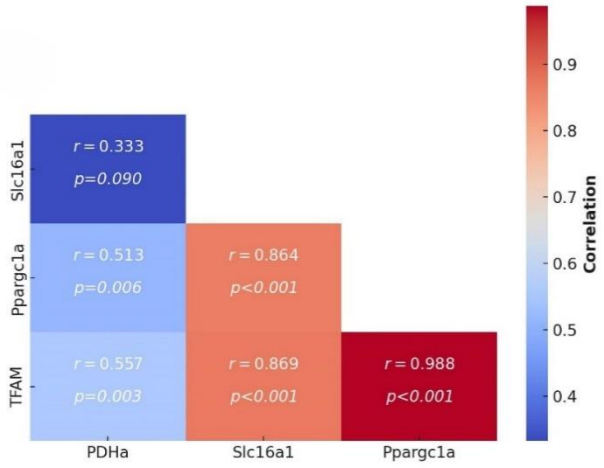
Figure I. PDHa and Slc16a1 Levels in Experimental Groups.



Median (IQR). *: p<0.05. Abbreviations: RJ: Royal Jelly, PDHa: Pyruvate Dehydrogenase Alpha, Slc16a1: Monocarboxylate Transporter 1.

The correlations between PDHa, Slc16a1, Ppargc1a, and TFAM levels are shown in Figure 2. A positive correlation was found between all parameters. As seen in the heatmap matrix, a very high level of positive correlation was found between Slc16a1 and TFAM and Ppargc1a (rho= 0.869, p<0.001; rho= 0.864, p<0.001, respectively). Also, the high correlation between TFAM and Ppargc1a, which are components of the same physiological mechanism (mitochondrial biogenesis), confirms our study results (rho= 0.98, p<0.001).

Figure 2. Heatmap Matrix Showing The Correlative Relationship Between The Parameters



Abbreviations: PDHa: Pyruvate Dehydrogenase Alpha, Slc16a1: Monocarboxylate Transporter 1, Ppargc1a: Peroxisome Proliferator-Activated Receptor Gamma Coaktivator 1-Alpha, TFAM: Transcription Factor A, Mitochondrial.

DISCUSSION

This study aimed to elucidate the effects of royal jelly supplementation on metabolic parameters by comparing them with control, royal jelly group, exercise and royal jelly+exercise groups. The findings showed that royal jelly supplementation decreased PDHa, a critical junction for aerobic respiration, whereas it significantly increased PDHa when taken in conjunction with acute exhaustive exercise. This suggests that royal jelly restores and improves the aerobic respiratory pathway during acute exhaustion exercise. Additionally, royal jelly supplementation increased the levels of Slc16a1 (MCT-1), which catalyzes the proton-coupled transport of monocarboxylates (I-lactate, pyruvate, and ketone bodies) across the plasma membrane. The level of Slc16a1, which decreased with acute exhaustion exercise, increased in the RJ+Exercise group. This finding suggests that royal jelly also activates the anaerobic respiratory pathway during acute exhaustion exercise. Correlation coefficients between Slc16a1 and PDHa levels and mitochondrial biogenesis parameters support the hypothesis about the aerobic and anaerobic mechanism of royal jelly.

Exercise is a fundamental component of cardiac rehabilitation regimens, and in particular, it reduces the risk of cardiovascular disease (9,10), supports general metabolic health (11), establishes and maintains musculoskeletal function (12), improves mental health (13), and extends life (14). The repeated deviations and changes in whole-body homeostasis caused by exercise cause different adaptations in various organs, including the brain, liver, adipose tissue, skeletal muscle, and heart (12,15). These effects may vary depending on the type of exercise (aerobic, anaerobic exercise), intensity, duration and physiological state (16). However, the molecular mechanisms by which exercise primarily improves cardiovascular health and prevents tissue injury remain unclear.

Low-intensity, rhythmic endurance-enhancing exercises involving larger muscle groups are defined as aerobic exercises (17), while short-term, high-intensity, and more strengthening exercises are defined as anaerobic exercises (18). In both types of exercise, skeletal muscle is one of the first organs to respond to homeostatic changes in adaptation to exercise and is critical for the effectiveness of exercise (19). One of the most important factors in muscle tissue during exercise is oxygen availability, which determines carbohydrate (Pyruvate) and lactate metabolism (20). Therefore, the preference of aerobic and anaerobic metabolic pathways of muscle tissue depends on this. Pyruvate dehydrogenase enzyme, one of the regulatory enzymes of carbohydrate metabolism, is regulated by the increase in ADP and pyruvate concentrations during exercise (21). It has been shown that pyruvate dehydrogenase enzyme activity increases during aerobic, sprint and isometric exercise (22). In contrast, in our study, PDHa activity was found to be low in muscle tissue after acute exhaustion exercise. This decrease is thought to be due to the active anaerobic metabolic pathway during acute exercise. However, RJ+exercise combination caused an increase in PDHa activity. This suggests that royal jelly enhances and improves the aerobic respiratory pathway during acute exhaustion exercise.

The production and utilization of lactate in muscles are strongly related to exercise performance. Increased accumulation of lactate in muscle tissue under hypoxic conditions or muscle disorders can lead to muscle fatigue and exercise intolerance (20). A decrease in pH and a significant increase in blood lactate concentration are just some of the negative effects that affect homeostasis, muscle contraction, strength, and ultimately exercise ability. On the other hand, lactate can be an important source of energy in working muscles. During exercise, it is critical to select an appropriate training intensity to maintain lactate balance and increase aerobic capacity (23). In addition, the presence and activity of certain enzymes (e.g. lactate dehydrogenase) or carrier proteins (Slc16a1/MCT1, MCT4) strongly determine the rate of lactate metabolism. Slc16a1, a proton-linked monocarboxylate transporter, facilitates rapid transfer of lactate across the cell membrane, which can be used as fuel for mitochondrial respiration in muscle tissue (24). It was found that royal jelly supplementation increased Slc16a1 levels in muscle tissue, while acute exhaustion exercise decreased Slc16a1 levels in muscle tissue. This shows that intramuscular lactate concentration increases in acute exhaustion exercise, and the lactate gradient is disrupted. However, it was found that Slc1a61 levels increased in the RJ+exercise group. Royal jelly supplementation has been shown to regulate lactate metabolism with acute exercise and to use lactate in the energy pathway.

Mitochondrial biogenesis is defined as the development of existing mitochondria and the adaptation of skeletal muscle to exercise training, induced by many signaling pathways that respond to metabolic, mechanical and hypoxic stresses occurring in myocytes during contraction (25). It has been determined that muscle mitochondrial biogenesis increases with regular exercise, and the increase in mitochondrial content increases endurance performance in individuals (26,27). It has also been reported that supplements that regulate energy metabolism contribute to this process with exercise (16). In contrast to endurance exercises, it has been reported that there is a decrease in mitochondrial volume in resistance exercises, thus decreasing mitochondrial biogenesis (28). On the other hand, some studies have stated that there is no increase or change in mitochondrial biogenesis or oxidative capacity markers after resistance exercise training (29,30) However, uncertainties on this issue still persist (31). In our study, it was found that Ppargc1a and TFAM levels, which are mitochondrial biogenesis markers, decreased after acute exhaustion exercise. Although not statistically significant, royal jelly supplementation increased mitochondrial biogenesis with exercise. Similarly, Flockhart et al. reported that excessive exercise leads to impairments in mitochondrial respiratory capacity (32). Another study indicated that short-term excessive exercise causes oxidative alterations in mitochondrial proteins, resulting in a significant reduction in mitochondrial respiration (33). These findings support the outcomes of our study. In addition, the high correlation coefficients between Slc16a1 and PDHa levels and mitochondrial biogenesis parameters support our hypothesis that royal jelly improves and regulates aerobic and anaerobic mechanisms. In general terms, the presence of varied outcomes in the literature may stem from differences in muscle activity protocols and the timing of post-exercise sample collection.

CONCLUSION

Our research emphasizes the impact of royal jelly on PDHa and Slc16a1 levels, which are crucial in the aerobic and anaerobic energy pathways. By supplementing with royal jelly, we observed an improvement in the regulation of these pathways during acute exhaustive exercise. Our findings have implications for various disciplines including exercise physiology and sports science.

Limitations and Suggestions for Future Research

Despite our contributions, there are some limitations to our research. Biochemical data along with the metabolic parameters used in this study could have contributed to the research results. Future studies can facilitate the evaluation with different tissues and a wide range of parameters to show the effects of acute exhaustion exercise and the effects of royal jelly-like supplements.

DESCRIPTIONS

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