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The effect of eight weeks of resistance training with spirulina platensis supplementation on the RAGs/Rheb/mTORC/S6K pathway in male rat kidneys

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Abstract

Background: Resistance training and protein supplementation are known to increase protein synthesis and hypertrophy, primarily through the activation of the mTORC1 signaling pathway. However, mTORC1 activation in the kidneys can potentially lead to kidney disease. This study investigates the effects of eight weeks of resistance training combined with Spirulina platensis supplementation on the RAGs/Rheb/mTOR/S6K pathway in male rat kidneys.

Methods: In this study, 32 male Sprague-Dawley rats were divided into four groups: control (Co; n = 8), Spirulina platensis (SP; n = 8), resistance training (RE; n = 8), and Spirulina platensis + resistance training (SP+RE; n = 8). The resistance training group engaged in five sessions per week over eight weeks. Spirulina was administered at a dosage of 200 mg/kg/day to the supplement and SP+RE groups. Gene expression was analyzed using real-time PCR following the last training session.

Results: The mTOR gene expression significantly increased in the SP group (p-value = 0.01), while no significant changes were observed in the RE and SP+RE groups. Rheb gene expression did not show significant changes across any groups. Significant changes were noted in the RAGs gene in the SP group (p-value = 0.001), RE group (p-value = 0.047), and SP+RE group (p-value = 0.025). The S6K gene showed significant changes in the SP group (p = 0.01) but not in the other groups.

Conclusion: Spirulina supplementation may activate the mTORC1 signaling pathway in the kidneys, potentially contributing to kidney disease progression. However, combined resistance training and Spirulina supplementation did not show changes in mTORC1 expression, suggesting that this combination might prevent further kidney tissue damage in athletes.

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Highlights

What is current knowledge?

Spirulina supplementation along with resistance training can prevent further damage to kidney tissue by inhibiting the pathways involved in increasing mTOR and Spirulina supplementation cause an increase in expression of mTOR, RAGs and S6k.

What is new here?

Since the RAGs is the mediators to activate the mTOR pathway, and mTOR along with S6k can develop the polycystic kidney disease and diabetic nephropathy, it is not recommended to use this supplement alone in kidney patients.

Introduction

The impact of supplements and exercise on health and safety has been relatively underexplored. Nevertheless, some studies have reported adverse effects of certain exercise supplements on kidney function (1). Spirulina, a blue-green alga that thrives in tropical and subtropical waters rich in carbonate and bicarbonate, boasts a high protein content ranging from 50% to 71% (2,3). Consumption of spirulina is known to reduce protein breakdown and enhance its synthesis, making it a recommended supplement for restoring body weight and muscle protein. Research indicates that combining spirulina with exercise significantly enhances isometric strength and endurance (4,5). Resistance training, a potent method for increasing muscle mass, is also a stimulus for altering homeostasis in skeletal muscle (6).

mTOR is a serine/threonine kinase that promotes protein synthesis and ribosome biogenesis while inhibiting a form of protein breakdown known as autophagy in some cells. Additionally, mTOR facilitates cell division and the transcription of certain genes (7,8). The phosphorylation of p70S6K, crucial for protein synthesis, occurs within the mTOR signaling pathway. p70S6K is a component of the mTORC1 signaling pathway (9). Various methods can activate mTORC1, but they all eventually activate mTOR through a small G-protein called Rheb (Ras homolog enriched in the brain). Rheb is believed to activate mTOR by recruiting phospholipase and increasing phosphatidic acid levels (8,10). mTOR regulates protein synthesis and cell growth by phosphorylating and thereby activating the 70 kDa ribosomal S6 kinase (p70S6K), which plays a regulatory role in protein synthesis and cell growth by phosphorylating its primary substrate, ribosomal protein S6, upon mitogen stimulation. Increased expression/activation of p70S6K is associated with poor prognosis in certain disease types, suggesting it may serve as a biomarker for some conditions (11).

Amino acids activate mTOR through small G-proteins called Rags. Since increased protein synthesis is a primary cause of hypertrophy and mTOR is central to protein synthesis, resistance training may induce hypertrophy by activating this pathway. It has been demonstrated that mTOR increases in response to resistance training (10). The mTOR signaling pathway plays a significant role in kidney tissue, contributing to the transformation of mesenchymal cells into epithelial cells and increasing the length of nephrons during development. This pathway is involved in various pathological processes in adulthood, including renal fibrosis from acute kidney injuries, renal cysts, and chronic kidney failure. Mice with deletions in some pathways of this signal at birth exhibit severe kidney defects (12). Exercise regulates the mTOR signaling pathway through several upstream mechanisms, and physical activity has been shown to activate some pathways in diabetic rats by increasing GSK-3β phosphorylation. Thus, exercise under diabetic conditions can influence the catenin-β/Wnt pathway by reducing GSK-3β gene expression, leading to decreased glucose levels and increased insulin levels in diabetic rats (13).

Pharmaceutical and dietary supplements can impact internal tissues, particularly the kidneys. For instance, protein supplements reportedly do not adversely affect kidney function (14). However, some studies suggest a relationship between dietary patterns and kidney function (15). It has been observed that a diet high in meat, seafood, and eggs negatively impacts kidney function, whereas diets rich in sausage, fruit, or dairy products improve kidney function (15). Additionally, improper creatine consumption can harm kidney function, although creatine taken with exercise results in less kidney damage than creatine taken alone (16). Research indicates that high-protein supplements combined with resistance training do not negatively affect kidney function. For example, a study demonstrated that high-protein intake with resistance training does not impair kidney function, although a high-protein diet alone affects the glomerular filtration rate and is linked to kidney damage (17).

Given that resistance training regulates protein synthesis and induces hypertrophy through mechanisms such as mTOR activation, and considering spirulina's high protein content and its ability to enhance protein synthesis, spirulina could potentially activate the mTOR pathway. Studies have shown that activating the mTOR pathway and increasing its expression can exacerbate kidney disease (18). Recent studies have emphasized the importance of mTOR activation in cell proliferation and cyst growth in polycystic kidney disease. Abnormal regulation of mTOR, phosphorylated S6K (P-S6K), and

phosphorylated S6 (P-S6) levels has been observed in the renal cysts of rats with autosomal dominant polycystic kidney disease (ADPKD) (19). Inhibition of mTOR and related signals reduced cyst growth and kidney enlargement, preserving kidney function in rats (19). Despite previous studies not addressing the effect of spirulina supplements on the mTOR pathway affecting kidney tissue, and ambiguous results regarding the impact of physical exercise, this study aims to evaluate the effect of eight weeks of resistance training with Spirulina platensis supplementation on the RAGs/Rheb/mTORC1/S6K pathway in the kidney tissue of soft rats.

Methods

Study design

The statistical population of this study consisted of male Sprague-Dawley rats. Thirty-two young male rats, aged 3 months with a mean weight of 290 ± 20 g, were selected. Throughout the study period, each rat was housed in a separate transparent polycarbonate cage in an environment maintained at a temperature of 22 ± 2°C, humidity of 55 ± 4%, and a 12:12 hour light-dark cycle. All animals had free access to standard rat food (Rat pellets prepared by Behparvar Company) and safe water and were cared for in accordance with relevant guidelines. The rats were grouped and, after the training period, were sacrificed to measure the desired factors.

Experimental animal groups

Initially, the rats were kept in the laboratory for a week to adapt to the environment. After one week of adaptation, the rats were introduced to resistance training and climbing the ladder once a day for 3 days. The ladder used was one meter high with a perpendicular slope to the ground, and the distance between steps was 4 cm. To encourage the rats to climb, their tails were gently touched to prompt movement. The introductory program involved three sessions of ladder climbing, each session comprising three to four repetitions without weights, conducted over one week. Following the introduction phase, the rats were randomly divided into the following four groups (8 rats in each group):

Group A: Control group (No resistance training, no spirulina supplementation)
Group B: Supplement group (No resistance training, spirulina supplement)
Group C: Resistance training group (No spirulina supplement)
Group D: Resistance training + Supplement group (Spirulina supplement)

Resistance training protocol

The resistance training protocol consisted of eight weeks of climbing a resistance training ladder. Each session began with a warm-up involving three repetitions without weights, with rest intervals between repetitions. The initial weight was set at 30% of the rats' body weight, gradually increasing to 100% by the final week. At the beginning of each week, the average weight of each group was measured, and weights were selected accordingly. During training sessions, weights were attached to the rats' tails using leucoplast adhesive. The training load consisted of 50%, 75%, 90%, and 100% of the selected weight for that week. Each training session included 3 sets of 5 repetitions with 1-minute rest between repetitions and 2 minutes rest between sets.

Spirulina supplementation

Spirulina was added to the drinking water of rats in the spirulina supplement groups (Groups B and D) at a dose of 200 mg/kg/day, starting 24 hours before the study and continued daily until the end of the eighth week.

Sampling

Twenty-four hours after the final training session, all rats were anesthetized with an injection of ketamine 10% (50 mg/kg body weight) and xylazine 2% (10 mg/kg body weight) for about five minutes and then decapitated. The kidneys were immediately removed, placed in nitrogen tanks, and transferred to an 80-degree freezer for RNA extraction. RT-PCR was used to measure the expression of Rheb, RAGs, mTOR, and p70S6K genes.

Statistical analysis

The Shapiro-Wilk test was used to assess the distribution of data within the research groups. The assumption of normality was confirmed, and a two-way ANOVA (SPSS version 18) was employed to examine the effects of interventions at a significance level of $P < 0.05$.

Results

Animal body weight and Rheb, RAGs, mTOR, p70S6K

Changes in animal weight and the expression levels of Rheb, RAGs, mTOR, and p70S6K in the Spirulina (SP), Resistance Exercise (RE), Spirulina + Resistance Exercise (SP + RE), and control (CO) groups are shown in Table 1. The results indicate that, after eight weeks, the body weight of rats increased in all groups (CO, SP, RE, and SP + RE).

mTOR changes

The expression of mTOR changed significantly across the groups by the end of the study period. Specifically, mTOR expression increased significantly in the SP group (p-value = 0.01), decreased non-significantly in the RE group (p-value = 0.16), and increased non-significantly in the RE + SP group (p-value = 0.06) (Table 2; Fig. 1A).

p70S6K changes

The expression of p70S6K also varied among the groups. There was a significant increase in p70S6K expression in the SP group (p-value = 0.044), while the changes in the RE + SP group (p-value = 0.37) and the RE group (p-value = 0.16) were not significant (Table 2; Fig. 1B).

RAGs changes

The expression of RAGs significantly increased in all experimental groups. The RE group (p-value = 0.047), the RE + SP group (p-value = 0.025), and the SP group (p-value = 0.001) all showed significant increases in RAGs expression (Table 2; Fig. 1C).

Rheb changes

The expression of Rheb did not change significantly in any of the groups by the end of the study period. The expression levels in the RE group (p-value = 0.13), SP + RE group (p-value = 0.70), and SP group (p-value = 0.28) were not significant (Table 2; Fig. 1D).

Table 1. Comparison of the effects of spirulina, resistance exercise, or spirulina + resistance exercise on changes in rat weight and expression levels of Rheb, RAGs, mTOR, and p70S6K after the experimental study

Parameter		Group			
		CO	SP	RE	SP + RE
Rat weight (gr)	Week 1	149.75 ± 5.14	151.62 ± 6.82	147.12 ± 15.83	149.12 ± 13.68
	Week 8	227.75 ± 6.71*	211.12 ± 13.84*	257.28 ± 12.22*	242.57 ± 5.19*
Rheb		1 ± 1.32	0.73 ± 0.56	0.86 ± 0.34	0.98 ± 0.49
RAGs		1 ± 0.58	7.26 ± 1.96	2.15 ± 1.05	1.55 ± 0.60
mTOR		1 ± 1.32	1.96 ± 0.80	0.86 ± 0.33	1.53 ± 0.31
P70S6K		1 ± 0.82	2.56 ± 1.75	1.91 ± 0.84	1.77 ± 1.45

CO; Control, SP; Spirulina, RE; Resistance Exercise, SP +RE; Spirulina + Resistance Exercise.
*p-value less than 0.05 considered as significant.

Table 2. Results of two-way analysis of variance to evaluate the effects of training and consumption of spirulina on Rheb, RAGs, mTOR, p70S6K in the kidney tissues of male rats

Parameter	Groups	Mean Square	F	P
RAGs	SP	109.44	105.51	0.001*
	RE	3.66	6.22	0.047*
	RE + SP	8.76	9.45	0.025*
Rheb	SP	0.62	1.40	0.28
	RE	0.45	3.02	0.13
	RE + SP	0.05	0.15	0.70
mTOR	SP	2.95	13.26	0.01*
	RE	0.14	2.44	0.16
	RE + SP	0.65	5.37	0.06*
P70S6K	SP	6.35	3.88	0.044*
	RE	2.43	2.50	0.16
	RE + SP	1.83	0.90	0.37

* P-value ≤0.05 is considered as significant

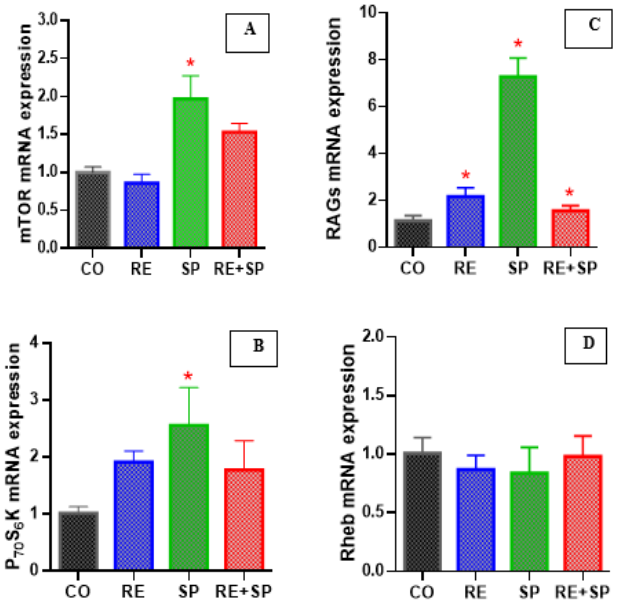

Figure 1. The effects of Spirulina (SP), Resistance Exercise (RE), and Spirulina + Resistance Exercise (SP + RE) on the expression of RAGs (part A), Rheb (part B), mTOR (part C), and p70S6K (part D) in the kidney. CO: control; SP: Spirulina platensis; RE: resistance exercise; SP + RE: Spirulina platensis + resistance exercise. Data are presented as the mean ± standard error of the mean. *P-value ⩽0.05 is considered significant.

Discussion

The aim of this study was to investigate the effect of eight weeks of resistance training with Spirulina platensis supplementation on the RAGs/Rheb/mTORC/p70S6K pathway in male rats. The main findings indicate that mTOR gene expression significantly increased only in the supplement group. In contrast, significant changes in RAGs gene expression were observed in the supplementation group, resistance training group, and the training + supplementation group. However, Rheb gene expression changes were not significant in any of the groups, and significant changes in p70S6K gene expression were observed only in the supplement group.

The significant increase in mTOR gene expression in the spirulina supplement group, but not in the resistance training or training + supplementation groups, contrasts with some previous studies. For example, Nemati et al. (2016) (20) and Sharafati Moghadam et al. (2018) (21) reported significant increases in mTOR gene expression in the skeletal muscles of diabetic rats. Conversely, Haraguchi et al. (2013) (22) found that resistance training did not significantly change mTOR gene expression in rats. This discrepancy might be due to the influence of regulated in development and DNA damage response 1 (REDD1) on the mTOR protein synthesis pathway. Increased REDD1 protein expression can decrease mTOR gene expression (23). Additionally, low-intensity physical activity can increase negative regulators of protein synthesis such as AMPK and 4E-BP1, with AMPK preventing mTOR activation by activating the TSC1/2 complex (24). Luciano et al. (2017) demonstrated that high-intensity hypertrophy resistance training was more effective than low-intensity endurance training in activating mTOR (25). The intensity of the exercise program in this study may not have been sufficient to significantly increase mTOR gene expression.

Nutrition, particularly protein intake, can increase serum amino acid levels, which are crucial for mTOR activation (26). Spirulina, rich in amino acids and antioxidants, appears to be a potent activator of mTOR and the autophagy process. The significant increase in mTOR gene expression observed only in the spirulina supplement group suggests that the supplement dosage might not be suitable for diabetic patients. Spirulina contains essential amino acids, including leucine, which can stimulate mTOR activation (27). Amino acids activate mTOR through RAGs independently of other activators. In this study, resistance training and resistance training with spirulina supplementation did not significantly increase mTOR gene expression, likely due to insufficient Rheb activation. Rheb is crucial for S6K and mTOR communication, and mTOR inhibitors can disrupt this communication through TSC activation (28). Many inhibitors, such as AMPK, can interrupt this communication (24). Therefore, while spirulina supplementation alone may be harmful to kidney patients, combining it with resistance training may mitigate this risk, as a significant increase in mTOR was not observed in the training or combined groups.

RAGs gene expression significantly changed in all experimental groups, consistent with the findings of Kim et al. (2008) and Sancka et al. (2008) (29,30). Kim et al. (2008) reported that in mammalian cells, constitutively active (GTP-bound) Rag activated TORC1 in the presence of amino acids, suggesting that spirulina's amino acid content led to increased RAGs expression. However, Rheb gene expression did not significantly change in any of the research groups, contrasting with Song et al. (2017) (31). Resistance training maintains or improves cell survival by activating growth factors, which in turn activate PI3K and AKT, regulating cell function through downstream proteins including mTOR (32). Two small GTPases, Rheb and Rags, activate mTOR in response to growth factors and amino acids, respectively (33). In this study, spirulina's amino acids likely increased RAGs expression, leading to mTOR activation in the supplement group. However, the inability to significantly increase mTOR gene expression in the resistance training and training + supplementation groups suggests that Rheb activation was insufficient. This finding is inconsistent with Ma and Blenis (2009), who identified Rheb as the primary factor in mTOR activation, as mTOR increased significantly in the spirulina group without a significant increase in Rheb (34). Increased mTOR activity is known to contribute to kidney tubular damage (33). The activation of this gene following supplementation might not yield positive outcomes, necessitating further studies with different dosages. The significant increase in mTOR and RAGs expression in the spirulina group, potentially harmful in kidney diseases such as polycystic kidney disease and nephropathy, requires careful consideration. However, the combined use of spirulina and resistance training appears less harmful, as indicated by the lack of significant changes in both mTOR and RAGs expressions. Nonetheless, research has indicated that in humans, 70S6K can be activated by Akt-independent pathways, and mTOR can be activated through various signaling mechanisms. Therefore, a comprehensive understanding of these processes in kidney tissue necessitates additional research (35). Given the role of S6K in the downstream pathway of mTOR signaling, its significant increase in the supplement group alone indicates that spirulina supplementation may be dangerous for kidney patients without the mitigating effect of resistance training.

The significant increase in p70S6K gene expression only in the spirulina supplement group aligns with findings from Sadeghipour et al. (2024), who reported significant increases in S6K gene expression following combined resistance training and spirulina supplementation (36). Mirzaei et al. (2023) observed significant decreases in S6K1 protein content in cardiac tissue after a 2-week resistance and aerobic training program, but gene expression analysis showed significant increases in S6K1 gene expression (37). Mousavi Muzafar (2020) reported significant differences in S6K levels across all three groups in a study on the effects of beta-hydroxy beta-methylbutyrate (HMB) supplementation and resistance training (38). The present study's findings contrast with those of Dreyer, Fujita et al. (2010) (39) and Hulmi, Tannerstedt et al. (2009) (40), but Haraguchi et al. (2014) observed increased mTOR expression with whey protein consumption, while exercise reduced mTOR expression (22). Amiri et al. (2019) found that HMB supplementation decreased myostatin and increased S6K gene levels, with greater effects when combined with resistance training (41). In this study, significant increases in mTOR and S6K gene expression in the supplement group suggest that amino acids in spirulina activate S6K through an mTOR-independent pathway, potentially involving PDK1 and PIF (27). Recent studies indicate that resistance activity can activate S6K through an AKT-independent pathway (42).

Therefore, while spirulina supplementation alone may increase the expression of mTOR and S6K, potentially harmful to kidney tissue, combining it with resistance training may mitigate this risk. The increase in S6K gene expression in the supplement group indicates that spirulina supplementation alone might be dangerous for patients with polycystic kidney disease and nephropathy. However, further investigations are necessary to understand the impact of spirulina supplementation with resistance training on kidney tissue. The inability to control daily activities of the rats, stress on the rats, and lack of protein content evaluation of the investigated variables are limitations of the present study.

Conclusion

Based on the findings of this study, eight weeks of resistance training did not significantly affect the mTOR pathway. However, spirulina supplementation had a significant effect, increasing mTOR pathway activity. Notably, there was no significant increase in this pathway in the group that combined exercise with spirulina supplementation. The results indicated higher expression levels of mTOR, RAGs, and S6K genes in the spirulina group. Given that RAGs mediate the activation of the mTOR pathway via amino acids and considering the role of mTOR and S6K in the development of kidney diseases such as polycystic kidney disease and diabetic nephropathy, it is not recommended for this group of patients to use spirulina alone. However, since no significant increase in mTOR was observed in the combined exercise and spirulina group, it is possible that the benefits of spirulina could be harnessed in conjunction with resistance training without posing a risk to kidney patients. This hypothesis requires further investigation in human samples.

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Ethical statement

The study was approved by the Ethics Committee of Jahrom University of Medical Sciences and was carried out in strict accordance with the United States Institute of Animal Research guidelines for the care and use of laboratory animals (IR.JUMS.REC.1398.011).

Conflicts of interest

The authors declare that they have no conflicts of interest.

Author contributions

All authors equally contributed to the writing and revision of this paper.

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