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Effect of Aerobic Training Combined with Resveratrol on Spinal Cord IL-6, TNF-α, and Locomotor Recovery after Spinal Cord Injury in Rats

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Abstract

Study Design: Controlled experimental animal study.

Objectives: To investigate the effect of four weeks of aerobic treadmill training combined with resveratrol supplementation on spinal cord interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) levels and locomotor recovery in a rat model of spinal cord injury (SCI).

Setting: University-based exercise physiology and animal research laboratory, Bojnourd, Iran.

Methods: Thirty-six male Wistar rats were allocated to healthy, SCI-control, resveratrol, exercise, and resveratrol + exercise groups. SCI was induced via a standardized weight-drop contusion at T10, and, beginning 14 days post-injury, rats underwent 4 weeks of body-weight-supported treadmill training and/or daily intraperitoneal resveratrol (10 mg/kg). Locomotor recovery was assessed using the Basso-Beattie-Bresnahan (BBB) scale, and spinal cord IL-6 and TNF-α levels were measured by ELISA.

Results: SCI significantly elevated spinal cord IL-6 and TNF-α relative to healthy controls ($P < 0.05$). Resveratrol supplementation, alone and combined with exercise, significantly reduced spinal cord IL-6 relative to control, whereas exercise alone did not. The combined resveratrol + exercise group showed the most consistent anti-inflammatory profile, with significantly lower IL-6 than the exercise-alone group, and was the only intervention group with significantly reduced TNF-α. BBB scores improved significantly only in the exercise-containing groups.

Conclusions: Resveratrol and exercise appear to act through partially distinct mechanisms that combine to produce superior anti-inflammatory and functional outcomes after SCI, supporting their combined use as an adjunct, non-pharmacological rehabilitative strategy.

Sponsorship: None.

Introduction

Traumatic spinal cord injury (SCI) is among the leading causes of permanent disability (1). Depending on the severity and anatomical level of the injury, patients may experience a range of neurological deficits, including sensory loss and impaired bowel, bladder, sexual, and autonomic nervous system function, up to paralysis and death (2). Approximately 2 to 3 million people worldwide currently live with SCI, with an additional 250,000-500,000 new cases occurring each year (3). The leading causes of SCI include motor vehicle accidents (50%), falls and occupational accidents (30%), gunshot wounds or violent crime (11%), and sports-related injuries (9%) (1, 2). Beyond the direct costs of treating the injury itself, substantial secondary costs arise from complications such as pressure ulcers, bladder/bowel dysfunction, neuropathic pain, osteoporosis, deep vein thrombosis, cystitis, respiratory complications, pneumonia, emergency re-hospitalization, and spinal cord injury-induced immune deficiency syndrome (SCI-IDS) (4).

Pathologically, SCI comprises primary and secondary injury phases. The primary injury results from the initial traumatic impact, causing immediate and irreversible mechanical damage. This primary injury triggers a pathophysiological cascade encompassing the secondary injury phase. Secondary injury begins within minutes of the primary trauma and is divided into acute, subacute, and chronic stages (5, 6). The acute secondary injury stage is characterized by vascular injury, excitotoxicity, ionic imbalance, oxidative damage, inflammatory responses, and immune cell activation. Acute secondary injury progresses to the subacute stage, marked by neuronal apoptosis, Wallerian degeneration, reactive astrocyte activation, axonal remodeling, and glial scar formation. The subacute stage subsequently progresses to chronic secondary injury, characterized by cyst formation, axonal atrophy, and glial scar maturation (6). Inflammation is a fundamental mechanism operating throughout both the primary and secondary phases of SCI. This inflammatory response occurs acutely within minutes of the traumatic injury and can persist for days or, chronically, for months to years (7). This inflammatory process leads to neuronal apoptosis, increased lesion volume, and impaired functional recovery (8). Within hours to days following SCI, tissue damage can vary substantially, and control of inflammation plays a critical role in limiting this tissue injury (7). Kouda et al. (2012) demonstrated that baseline levels of inflammatory factors are higher in individuals with SCI than in healthy individuals (9).

Interleukin-6 (IL-6) is a pleiotropic cytokine involved in a broad range of biological processes, including various neuropathologies (10). IL-6 acts by binding to the IL-6 receptor (IL-6R), a process that enables the resulting complex to associate with the glycoprotein gp130. Trauma to the central nervous system substantially elevates IL-6 in both humans and animal models (11, 12). Previous reports indicate that IL-6 mRNA levels increase significantly as early as 6 hours after spinal cord injury (13). Most studies examining IL-6 in SCI have focused on acute changes occurring from hours to days post-injury (10, 12, 14). Mukaino et al. (2010) demonstrated that blocking acute IL-6 signaling with a neutralizing IL-6R antibody significantly improves motor recovery in SCI mice (15).

One cytokine that has been extensively studied following spinal cord injury is tumor necrosis factor-alpha (TNF-α) (16). TNF-α participates in tissue homeostasis and various physiological processes in the central nervous system, such as synaptic plasticity and learning and memory (17). However, TNF-α also plays a key role in inflammation, and its overproduction has been linked to various inflammatory CNS pathologies, including traumatic brain injury, stroke, Alzheimer's disease, multiple sclerosis, and SCI (17). In this regard, Lund et al. (2023), in a review article, noted that TNF-α plays an important role in the inflammatory response following spinal cord injury, suggesting that targeting TNF-α signaling is a feasible therapeutic approach for SCI (16).

Exercise training and the use of natural antioxidants are employed as alternative therapeutic approaches for various neurological injuries, including SCI (18). Resveratrol (3,4',5-trihydroxystilbene) is a natural plant polyphenol that has demonstrated potent antioxidant, anti-inflammatory, and anticarcinogenic pharmacological properties in previous studies (19). This supplement has been administered for the treatment of stroke and has shown positive clinical outcomes (20). Numerous studies have demonstrated that resveratrol can scavenge free radicals and is effective in inhibiting lipid peroxidation

and controlling the activity of oxidation-related enzymes (19). Furthermore, previous studies have established resveratrol's unique protective effect on the central nervous system; for example, it has been shown to enhance cognitive function and memory to varying degrees following brain injury (21). At the same time, resveratrol suppresses inflammation and stimulates neuronal recovery following central nervous system injury. Additionally, Zhao et al. (2017) reported that resveratrol exerts a neuroprotective effect by regulating apoptosis and autophagy following neural injury (22). Exercise training, meanwhile, has attracted researchers' attention as a non-pharmacological strategy for reducing complications arising from spinal cord injury (23). Aerobic training has been emphasized as one of the supportive treatments for SCI. The relationship between aerobic exercise and immune response has long been a topic of interest in the sports medicine community. Moderate-intensity aerobic exercise can activate the body's immune system. According to some studies, aerobic training can exert anti-inflammatory effects by regulating the expression of cytokines such as IL-6 and TNF-α (23).

Overall, the sequelae of SCI are exacerbated by the presence of inflammatory cells and pro-inflammatory cytokines. Inflammatory responses lead to apoptosis of neurons and oligodendrocytes, as well as scar tissue formation, ultimately reducing neurological function (1). Since one of the goals in treating SCI is to inhibit secondary injury at the lesion site and promote functional recovery of the limbs below it, and given the role of inflammation and oxidative stress in SCI pathogenesis, inhibiting oxidative stress and inflammation may represent an appropriate strategy for reducing SCI-related complications (1). Therefore, the aim of the present study was to investigate the effect of aerobic training combined with resveratrol supplementation on spinal cord tissue levels of IL-6 and TNF-α in rats with SCI.

Materials and Methods

The present study was an experimental, post-test-only design comprising one control group and three experimental groups. Thirty-six adult male Wistar rats, weighing 185–200 g and aged eight weeks, were purchased from the animal laboratory of North Khorasan University of Medical Sciences and housed accordingly. Rats were housed in groups of 3–4 under standard conditions (temperature 22 ± 3°C, 12-hour light-dark cycle, and standard humidity), with access to food and water, and in accordance with the guidelines of the Iranian Society for the Protection of Laboratory Animals. After acclimatization to the new environment and reaching the target body weight, animals were randomly assigned, stratified by body weight, to four groups of nine: (1) control (SCI only), (2) resveratrol, (3) exercise, and (4) resveratrol + exercise; animals then underwent surgery to induce spinal cord injury. No analgesia was administered following spinal cord injury surgery, but all animals received antibiotic treatment to prevent post-surgical infection. During the study, some animals died as a result of the surgical procedure, and others were subsequently excluded because of severe weakness or inability to continue the training protocol; final group sizes after these exclusions are reported in the Results (Tables 1 and 2).

Induction of Spinal Cord Injury

Once rats reached a body weight of 225 g, animals were anesthetized using a ketamine/xylazine mixture. The fur on the animal's back was then gently shaved, and the surgical site was disinfected. A midline incision was made over the vertebral prominences, and the muscles and lamina of the T9 vertebra were removed without damaging the dura mater. SCI was then induced by dropping a 10-gram weight from a height of 25 mm onto the spinal cord at the T10 segment (24).

Confirmation of Spinal Cord Injury

The Basso-Beattie-Bresnahan (BBB) scale was used to assess neurological function. The BBB scale is a 21-point scale, in which a score of 1 indicates no hindlimb movement, up to a score of 21, indicating normal hindlimb function. Scoring on this scale accounts for functional aspects of hindlimb performance, such as weight support, stepping ability, coordination, and toe clearance (24, 25). Scoring of SCI rats was performed by an independent, blinded expert.

Resveratrol Supplementation

Resveratrol supplement (Sigma) was dissolved in 50% ethanol. It was then dissolved daily in a solution consisting of 0.9% saline containing 20% hydroxypropyl-β-cyclodextrin (Sigma). This solution was administered intraperitoneally at a dose of 10 mg/kg daily. Rats in the other groups received an equivalent volume of saline (26).

Training Protocol

The exercise groups followed a training protocol using a treadmill in conjunction with a body-weight support system. Prior to SCI, all rats underwent two 30-minute sessions of acclimatization to the treadmill environment. To avoid exacerbating the secondary injury cascade, the training program began 14 days after injury and after BBB testing was performed. The exercise groups initially trained on the treadmill at a speed of 10 m/min for 20 minutes while wearing a supportive harness. Over the following 7 training days, as previously described, session duration was gradually increased from 20 minutes to a target of 58 minutes, and training intensity was increased to 20 m/min (27). The total training period was 4 weeks.

Rats were anesthetized 48 hours after the final training session. Anesthesia was induced via intraperitoneal injection of a combination of ketamine (60–80 mg/kg body weight) and xylazine (8 mg/kg body weight). Spinal cord tissue was carefully dissected from the injury site following skin cleaning and vertebral separation; after removal and clearing of blood, samples were transferred to coded cryotubes, snap-frozen in liquid nitrogen, and subsequently stored at -70°C. It should be noted that, at the end of the study protocol, 6 animals remained in the control group, 6 in the resveratrol group, 7 in the exercise group, and 7 in the resveratrol + exercise group.

Spinal cord IL-6 levels were measured using a DuoSet ELISA kit (catalog number DY506). Spinal cord TNF-α levels were likewise measured using a DuoSet ELISA kit (catalog number DY510).

Statistical Analysis

Sample size (nine animals per group at the outset) was based on conventional practice in comparable rodent spinal cord injury studies rather than an a priori power calculation. Following collection of raw data, the Shapiro-Wilk test was used to assess normality of distribution, and Levene's test was used to assess the assumption of equal variances. After confirming normal distribution and homogeneity of variance, one-way ANOVA and the LSD post hoc test were used for between-group statistical comparisons. All statistical calculations were performed using SPSS version 16 at a significance level of $P < 0.05$. Graphs were generated using Microsoft Excel 2013. The study protocol was not pre-registered.

Use of Artificial Intelligence

An AI language tool was used to assist with translating the manuscript into English and with drafting the Discussion and Conclusion section based on the authors' data, study design, and cited literature. All AI-assisted content was reviewed, verified, and edited by the authors, who take full responsibility for the accuracy, integrity, and originality of the manuscript.

Results

Effect of Training and Resveratrol on the BBB Scale

Data on the BBB scale of rats at baseline and after 4 weeks of aerobic training and resveratrol supplementation are presented in Table 1. Because group assignment was based on BBB score, no significant difference was observed in this index prior to the start of the study ($P = 0.819$). Results showed a significant difference in BBB scale scores between groups after 4 weeks of aerobic training and resveratrol supplementation ($P = 0.01$), such that this score was significantly higher in the exercise and resveratrol + exercise groups relative to both the pre-test and the control group ($P < 0.05$).

Table 1
BBB test results at pre-test and post-test across study groups.

Index	Stage	Control	Resveratrol	Exercise	Resveratrol + Exercise
BBB	Pre-test	12.25 ± 1.71	11.51 ± 2.38	11.61 ± 2.41	12.5 ± 1.91
	Post-test	12.51 ± 1.29	11.75 ± 1.98	15.79 ± 1.83 *&	16.25 ± 2.75 *&

** Significant difference vs. pre-test; & significant difference vs. control group.*

A one-way ANOVA and Tukey's post hoc test were used to compare spinal cord IL-6 and TNF-α levels among the study groups of SCI rats. Table 2 presents the one-way ANOVA findings comparing the effect

of aerobic training and resveratrol supplementation on spinal cord IL-6 and TNF-α levels across the study groups.

Table 2
Comparison of spinal cord IL-6 and TNF-α levels across study groups and one-way ANOVA findings.

Index	Healthy	Control	Resveratrol	Exercise	Exercise + Resveratrol	F	P
IL-6 (pg/mg)	47.08 ± 7.22	119.86 ± 22.01	87.31 ± 21.87	101.9 ± 12.49	57.08 ± 13.88	14.28	0.001*
TNF-α (pg/mg)	8.82 ± 2.6	21.21 ± 3.96	15.35 ± 3.47	13.69 ± 4.53	10.5 ± 3.65	5.884	0.005*

** Significant difference among study groups.*

One-way ANOVA findings indicated a significant difference in spinal cord IL-6 levels among SCI rats after 4 weeks of aerobic training and resveratrol supplementation (F = 14.28, P = 0.001). Tukey's post hoc test showed that spinal cord IL-6 levels were significantly higher in the control group than in the healthy group (P = 0.001). This index was significantly lower in the resveratrol (P = 0.044) and exercise + resveratrol (P = 0.001) groups relative to the control group. However, no significant difference in this index was observed between the exercise group and either the control group (P = 0.488) or the resveratrol group (P = 0.627). Spinal cord IL-6 levels in the exercise + resveratrol group were significantly lower than in the exercise-alone group (P = 0.007), but did not differ significantly from the resveratrol-alone group (P = 0.066).

One-way ANOVA findings indicated a significant difference in spinal cord TNF-α levels among SCI rats after 4 weeks of aerobic training and resveratrol supplementation (F = 5.884, P = 0.005). Tukey's post hoc test showed that spinal cord TNF-α levels were significantly higher in the control group than in the healthy group (P = 0.005). No significant difference in this index relative to the control group was observed in the resveratrol (P = 0.067) or exercise (P = 0.245) groups. However, TNF-α levels in the exercise + resveratrol group were significantly lower than in the control group (P = 0.009). No significant difference in spinal cord TNF-α levels was observed among the exercise + resveratrol, exercise, and resveratrol groups (P > 0.05).

Discussion and Conclusion

The present study aimed to determine whether 4 weeks of aerobic treadmill training, alone or combined with resveratrol supplementation, could modify spinal cord IL-6 and TNF-α levels and improve locomotor recovery in a rat contusion model of SCI. Three principal findings emerged. First, SCI produced the expected inflammatory phenotype, with significantly elevated spinal cord IL-6 and TNF-α in the untreated control group relative to healthy animals, consistent with the well-documented acute and sustained pro-inflammatory cytokine response that follows contusive spinal cord trauma (7–9, 11–14). Second, resveratrol supplementation, whether alone or combined with exercise, was the intervention most

consistently associated with lower spinal cord cytokine levels, whereas exercise alone did not significantly lower either cytokine relative to control. Third, and most notably, the combination of exercise and resveratrol produced the most consistent anti-inflammatory profile and, unlike resveratrol alone, was also accompanied by significantly improved BBB locomotor scores — a functional benefit that exercise-containing groups, but not the resveratrol-only group, achieved.

The dissociation observed here — in which locomotor recovery tracked with exercise exposure, while cytokine suppression tracked more closely with resveratrol exposure — suggests that these two interventions may act through at least partially distinct mechanisms that converge advantageously when combined. Aerobic treadmill training with body-weight support is thought to promote functional recovery after SCI primarily through activity-dependent mechanisms below the lesion, including enhanced spinal locomotor circuit excitability, use-dependent plasticity of surviving descending and propriospinal pathways, and improved neuromuscular activation, effects that can occur without necessarily normalizing local pro-inflammatory cytokine levels within the injury epicenter (23, 27). This may explain why exercise alone significantly improved BBB scores without significantly lowering IL-6 or TNF-α relative to control in the present study.

The absence of a significant independent effect of exercise on spinal cord IL-6 also merits a more specific mechanistic explanation. Skeletal muscle contraction itself acutely releases substantial IL-6 as a “myokine” — a response driven by calcium signaling and glycogen depletion rather than by immune-cell activation — and this muscle-derived IL-6 has been shown to exert net anti-inflammatory, rather than pro-inflammatory, downstream effects, including suppression of TNF-α production and induction of IL-10 and IL-1 receptor antagonist (28). This “IL-6 paradox” means that the pathological, sustained elevation of spinal cord IL-6 measured here at a fixed time point 48 hours after the final training session, several weeks after injury, is mechanistically distinct from the acute, adaptive myokine response to a single bout of exercise, and the two should not be assumed to move in the same direction. It is therefore plausible that chronic aerobic training modulates systemic and local inflammatory tone through this myokine-mediated pathway without necessarily producing a large, statistically detectable reduction in tissue IL-6 at a single late time point, particularly at the sample sizes available here.

Resveratrol, in contrast, is a well-characterized direct modulator of inflammatory and redox signaling within spinal cord tissue itself. Its anti-inflammatory action has been attributed principally to inhibition of NF-κB-dependent transcription of pro-inflammatory cytokines, together with activation of SIRT1, which deacetylates the NF-κB subunit p65 and thereby represses its transcriptional activity, as well as activation of AMPK and scavenging of reactive oxygen species (19, 22, 29, 30). Zhao et al. (2017, 2021) demonstrated in rat SCI models that resveratrol confers neuroprotection and promotes motor recovery specifically through SIRT-1/NF-κB- and SIRT1/AMPK-mediated suppression of TNF-α, IL-1β, and IL-6, alongside reduced motor neuron loss (22, 29), and Xu et al. (2018) similarly identified NF-κB inhibition as the central mechanism linking resveratrol to reduced inflammation, oxidative damage, and apoptosis after SCI (30). These direct, tissue-level mechanisms are well-positioned to explain the significant reduction in spinal cord IL-6 observed in the resveratrol-treated groups in the present study, independent

of the indirect, systemic myokine pathway through which exercise is thought to act. This interpretation is further supported by our group's related work in the same SCI model, which showed that combined aerobic training and resveratrol supplementation significantly increased SIRT1 and PGC-1α levels in the gastrocnemius muscle of SCI rats (23) — consistent with the hypothesis that SIRT1 pathway activation, driven substantially by resveratrol, is a shared mechanism linking metabolic and anti-inflammatory adaptations across tissues in this model.

Why, then, did the combination of exercise and resveratrol outperform resveratrol alone on IL-6 specifically (P = 0.007 versus exercise), and was the only group to achieve a significant reduction in TNF-α? If exercise acts substantially through the systemic myokine/IL-10 axis (28) while resveratrol acts substantially through direct tissue-level SIRT1/NF-κB inhibition (22, 29, 30), these two mechanisms are largely non-redundant and would be expected to combine additively or synergistically rather than to duplicate one another — consistent with the superior anti-inflammatory profile of the combined group observed here. It is also plausible that exercise-induced improvements in local tissue perfusion and metabolic activity enhance resveratrol delivery or cellular uptake at the lesion site, further amplifying its direct anti-inflammatory action.

The parallel improvement in BBB locomotor scores in both the exercise and exercise + resveratrol groups, but not in the resveratrol-alone group, reinforces the interpretation that motor recovery in this model depends substantially on activity-dependent neuromuscular and spinal circuit mechanisms that resveratrol alone, in the absence of loading and stepping practice, cannot fully replicate (23, 27). At the same time, the numerically greatest BBB improvement occurred in the exercise + resveratrol group, raising the possibility that resveratrol's suppression of local inflammation and oxidative stress may create a more permissive tissue environment for exercise-induced plasticity and repair, thereby modestly potentiating the functional benefit of training — a hypothesis that would require direct mechanistic testing (e.g., lesion volume, axonal sparing, or glial scar composition) to confirm.

These findings should be interpreted in light of several limitations. First, the relatively small number of animals surviving to the end of the protocol in each group (n = 6–7) limited statistical power, particularly for the TNF-α comparisons, where several pairwise differences approached but did not reach significance (e.g., resveratrol vs. control, P = 0.067) and may reflect a true, underpowered effect rather than a genuine null result. Second, cytokine levels were measured only at a single time point (48 hours after the final training session, several weeks post-injury), so the acute (hours-to-days) inflammatory trajectory following SCI, during which IL-6 and TNF-α are classically most dynamic (11–14), was not captured; measuring cytokines at additional time points would clarify whether training and resveratrol act primarily on the acute or the more sustained inflammatory phase. Third, the study assessed only two circulating/tissue cytokines and gross locomotor function; direct histological outcomes (lesion volume, glial scarring, neuronal and oligodendrocyte survival) and upstream signaling intermediates (e.g., NF-κB activation, SIRT1/AMPK phosphorylation) were not measured, limiting mechanistic attribution. Finally, as with all rodent contusion-SCI models, extrapolation to human SCI, which involves more heterogeneous injury mechanisms and a more protracted clinical course, should be made cautiously.

In conclusion, four weeks of resveratrol supplementation, particularly when combined with aerobic treadmill training, significantly reduced spinal cord IL-6 and TNF-α levels in a rat model of SCI, while functional locomotor recovery, as measured by the BBB scale, was driven primarily by exercise exposure. This pattern is consistent with two partially distinct but complementary mechanisms: a systemic, myokine-mediated anti-inflammatory pathway associated with exercise (28), and a direct, tissue-level SIRT1/NF-κB-dependent anti-inflammatory action of resveratrol within the spinal cord (22, 29, 30). The combined intervention produced the most favorable profile overall, achieving both significant anti-inflammatory and functional benefits, and outperformed either intervention alone on the IL-6 and TNF-α comparisons. These findings support combined aerobic exercise and resveratrol supplementation as a promising, non-pharmacological adjunct strategy for mitigating the neuroinflammatory sequelae of SCI and promoting functional recovery, while future studies incorporating additional time points, histological outcomes, and direct measurement of upstream signaling markers (NF-κB activation, SIRT1/AMPK phosphorylation, circulating myokine levels) are needed to more precisely delineate the mechanistic basis of this apparent synergy.

Declarations

Ethical Approval

This study was approved by the Ethics Committee of the Sport Sciences Research Institute of Iran, approval code IR.SSRC.REC.1402. All procedures involving animals were conducted in accordance with the guidelines of the Iranian Society for the Protection of Laboratory Animals.

Competing Interests

The authors declare no competing interests in relation to the work described in this manuscript.

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Author Contributions

HYA performed the laboratory experiments. AY supervised the study. MF wrote the manuscript. All authors read and approved the final manuscript.

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Data Availability Statement

The data generated and analyzed during the current study are available from the corresponding author on reasonable request.

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