Moderate-intensity training has a better effect on growth factors than high-intensity training in rats

El entrenamiento de intensidad moderada tiene un mejor efecto sobre los factores de crecimiento que el entrenamiento de alta intensidad en ratas

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Abstract

Introduction: Exercise is widely known to be a powerful stimulus to the endocrine system. Several previous studies have examined the effects of exercise on GH, melatonin, or cortisol separately. However, to date, no study has directly examined all three hormones simultaneously within a single exercise protocol, especially using a controlled rat models.
Objective: The study aims to determine the effect of moderate-intensity training and high-intensity training on growth determinants in rats.
Methodology: A total of 39 male rats, Rattus Norvegicus strain Wistar type, 8 weeks aged, 160±20 gram and randomly divided into three groups: CON (n = 13, controls without treatment), MIT (n = 13, moderate-intensity training, using a treadmill with a speed of 14-16 m/min for 30 minutes and HIT (n = 13, high-intensity training, using a treadmill at a speed of 22-25 m/min during 20 minutes). Treatment was carried out from 17.00-21.00 p.m. with a frequency of 3 times/week for 12 weeks. Blood was taken after 24 hours after the last exercise treatment. Serum measurements of growth hormone (GH), melatonin and cortisol using the ELISA. The data were analyzed by using one way-ANOVA and Tukey's HSD post hoc test with significant levels of 5%.
Results: We observed GH levels in CON (4.30 ± 0.29) pg/mL, MIT (4.55 ± 0.17) pg/mL, HIT (4.09 ± 0.28) pg/mL and ($p < 0.001$). Melatonin levels in CON (172.31 ± 15.86) pg/mL, MIT (193.54 ± 25.01) pg/mL, HIT (165.96 ± 15.44) pg/mL and ($p < 0.05$). Cortisol levels in CON (247.22 ± 50.26) ng/mL, MIT (212.82 ± 41.24) ng/mL, HIT (262.11 ± 19.56) ng/mL and ($p < 0.05$).
Conclusions: These findings suggest that moderate-intensity training has a better effect on growth determinants compared to high-intensity training in rats.

Keywords

Cortisol; growth hormone; melatonin; moderate-intensity training; high-intensity training.

Resumen

Introducción: Es bien sabido que el ejercicio es un potente estímulo para el sistema endocrino. Varios estudios previos han examinado los efectos del ejercicio sobre la GH, la melatonina o el cortisol por separado. Sin embargo, hasta la fecha, ningún estudio ha examinado directamente las tres hormonas simultáneamente en un solo protocolo de ejercicio, especialmente utilizando modelos controlados de ratas.
Objetivo: El estudio tiene como objetivo determinar el efecto del entrenamiento de intensidad moderada y del entrenamiento de alta intensidad sobre los determinantes del crecimiento en ratas.
Metodología: Un total de 39 ratas macho, Rattus Norvegicus cepa tipo Wistar, 8 semanas de edad, 160 ± 20 gramos y divididos aleatoriamente en tres grupos: CON (n = 13, controles sin tratamiento), MIT (n = 13, entrenamiento de intensidad moderada, utilizando una cinta de correr con una velocidad de 14-16 m/min durante 30 minutos y HIT (n = 13, entrenamiento de alta intensidad, utilizando una cinta de correr a una velocidad de 22-25 m/min durante 20 minutos). El tratamiento se llevó a cabo de 17:00 a 21:00 p.m. con una frecuencia de 3 veces por semana durante 12 semanas. Se extrajo sangre 24 horas después del último tratamiento de ejercicio. Mediciones séricas de hormona de crecimiento (GH), melatonina y cortisol utilizando ELISA. Los datos se analizaron mediante ANOVA de una vía y la prueba post hoc de HSD de Tukey con niveles de significancia del 5%.
Resultados: Observamos niveles de GH en CON (4,30 ± 0,29) pg/mL, MIT (4,55 ± 0,17) pg/mL, HIT (4,09 ± 0,28) pg/mL y ($p < 0{,}001$). Melatonina en CON (172,31 ± 15,86) pg/mL, MIT (193,54 ± 25,01) pg/mL, HIT (165,96 ± 15,44) pg/mL y ($p < 0{,}05$). Cortisol en CON (247,22 ± 50,26) ng/mL, MIT (212,82 ± 41,24) ng/mL, HIT (262,11 ± 19,56) ng/mL y ($p < 0{,}05$).
Conclusiones: Estos hallazgos sugieren que el entrenamiento de intensidad moderada tiene un mejor efecto sobre los determinantes del crecimiento en comparación con el entrenamiento de alta intensidad en ratas.

Palabras clave

Cortisol; hormona del crecimiento; melatonina; entrenamiento de intensidad moderada; entrenamiento de alta intensidad.

Introduction

Physiological adaptations to physical exercise involve complex interactions between various body systems, particularly the endocrine system, which regulates the body's response to stress and training loads. Among these hormonal factors, growth hormone (GH) plays a central role as a key mediator in linear growth, muscle tissue development, and anabolic metabolism (Donato et al., 2021). Melatonin, although primarily known for regulating circadian rhythms, has emerging relevance in muscle repair and antioxidative processes, particularly through its role in promoting mitochondrial integrity and cellular regeneration during rest phases (Kruk et al., 2021). Conversely, cortisol, the principal stress hormone, contributes to maintaining energy availability through catabolic activity. However, chronically elevated cortisol levels may impair growth, suppress immune responses, and contribute to metabolic dysregulation (Mashfufa et al., 2022). These hormones—GH, melatonin, and cortisol—function as part of an interconnected endocrine axis, where the balance between anabolic and catabolic signals is critical for optimal adaptation. For instance, moderate elevations in GH and melatonin, coupled with controlled cortisol levels, are associated with enhanced recovery and tissue regeneration. Conversely, excessive cortisol release, especially following high-intensity exercise, may inhibit GH action and dampen anabolic signaling (Caplin et al., 2021).

Physical exercise is widely recognized as a potent stimulus for the endocrine system. Research indicates that physical activity can enhance GH and melatonin secretion, while also significantly influencing cortisol levels, depending on the intensity of the exercise (Dharmasanti et al., 2024). Veldhuis and Weltman (2001), as well as Dharmasanti et al. (2024), reported that moderate-intensity exercise increases GH levels and reduces cortisol, reflecting a balanced physiological adaptation. On the other hand, high-intensity exercise does stimulate GH secretion but is also accompanied by a sharper spike in cortisol (Raastad et al., 2000), which, if it becomes chronic, may disrupt hormonal homeostasis (Caplin et al., 2021). Systematically comparing the effects of moderate- and high-intensity exercise is therefore important to determine the most hormonally beneficial intensity. This has practical implications for exercise program design, especially in the context of promoting growth and long-term physiological performance. In experimental contexts, the use of animal models such as Rattus norvegicus Wistar strain rats provides advantages in terms of variable control, biological replication, and similarities in neuroendocrine responses to physical training. Furthermore, the use of rats allows for more detailed biochemical and tissue evaluations, which are not always feasible in human subjects due to ethical constraints and invasive procedures (De Carvalho et al., 2022).

Several previous studies have examined the effects of exercise on GH, melatonin, or cortisol individually. However, to date, no research has directly observed all three hormones simultaneously within a single training protocol, especially using a controlled treadmill rat model. Studies by De Carvalho et al. (2022) and D'Haese et al. (2024) have compared exercise intensity in relation to metabolic biomarkers and cardioprotective effects, but have not specifically evaluated GH, melatonin, and cortisol in an integrated manner. Therefore, the mechanistic interplay between training intensity and concurrent hormonal fluctuations warrants deeper investigation. Therefore, this study aims to determine the effects of moderate- and high-intensity exercise on growth hormone, melatonin, and cortisol levels as key indicators of growth, using the Rattus norvegicus Wistar strain rat model. This research is expected to contribute scientifically to the development of evidence-based training programs that support hormonal balance and optimal physiological growth.

Method

Experimental design

This study employed a true experimental design using a randomized control group posttest-only design. A total of 39 male Rattus norvegicus Wistar strain rats (8 weeks old, weighing 160±20 grams) were randomly assigned to three groups: the control group (CON, no treatment), the moderate-intensity training group (14–16 m/min, 65–70% VO_2max), and the high-intensity training group (22–25 m/min, 80% VO_2max). Food pellets (BR-1, PT Japfa Comfeed, Indonesia Tbk) were given at 07.00 am as much as 40 grams/rats, and drinks were given as much as they wanted for 12 weeks. Acclimatization of experimental animals was carried out for seven days before the study began by placing them at a room temperature of 26 ± 2°C with a humidity level of 50-60%. The location where the experiment was conducted was at the Experimental Animal Laboratory, Department of Sports Science, Faculty of Sports Science, Universitas Negeri Malang (Indonesia). All procedures in this study were approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Brawijaya (Indonesia) [No:133/EC/KEPK-S1/05/2018]. The present study followed the animal welfare principles in experimental science as outlined in the European Convention for the Protection of Vertebrate Animals.

Exercise protocol

Moderate-intensity training (MIT) was conducted by having the rats run on a treadmill at a speed of 14–16 m/min (65-70% VO_{2max}) for 30 minutes, while high-intensity training (HIT) was performed at a speed of 22–25 m/min (80% VO_{2max}) for 20 minutes (Pranoto et al., 2020; Kim et al., 2013). The training sessions were carried out between 5:00–9:00 p.m., three times per week for a duration of 12 weeks (Pranoto et al., 2020). The workload of each group was equalizer based on the distance traveled on the treadmill. Meanwhile, the control group was allowed to carry out normal activities in the cage without receiving any intervention. Detailed training protocols are presented in Table 1.

Table 1. Moderate-Intensity Training and High-Intensity Training Protocols

Training Variables	MIT	HIT
Frequency	3 times/week	3 times/week
Intensity	65-70% VO_{2max}	80% VO_{2max}
Time	30 minutes/session	20 minutes/session
Type	Continuous	Continuous
Treadmill Speed	14 – 16 m/min	22 – 25 m/min

Biochemical analysis

Body weight and leftover food were measured before and after the final training session using a Harnic HL-3650 Heles digital scale (0–5 kg capacity). Blood samples for growth hormone (GH), melatonin, and cortisol measurements were collected 12 hours after the final MIT and HIT interventions over the 12 weeks as much as 3 ml (Puspita et al., 2025). All collected samples were centrifuged for 15 minutes at 3000 rpm to obtain serum samples. The collected serum samples were transferred into 1.5 ml eppendorf tubes and stored at -80°C for analysis the next day. GH levels were measured using the BT-Lab Enzyme-Linked Immunosorbent Assay Kit BT-E0551Ra (Biossays Technology Laboratory, Inc., China), with a standard curve range of 0.05–30 ng/mL and a sensitivity level of 0.024 ng/mL. Melatonin levels were measured using the BT-Lab ELISA Kit BT-E0601Ra (Biossays Technology Laboratory, Inc., China), with a standard curve range of 5–1000 ng/mL and a sensitivity of 2.5 ng/mL. Cortisol levels were measured using the BT-Lab ELISA Kit BT-E0828Ra (Biossays Technology Laboratory, Inc., China), with a standard curve range of 1–400 ng/mL and a sensitivity of 0.43 ng/mL.

Data analysis

Data analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software version 21.0 (Chicago, IL, USA). Data normality was tested using the Shapiro–Wilk test, while homogeneity was assessed using Levene's test. Normally distributed data with homogeneous variances were analyzed using one-way ANOVA, followed by Tukey's Honest Significant Difference (HSD) post hoc test. Pearson's correlation coefficient test was a used to test the correlation between variables. All data are presented as mean ± standard deviation (SD). Statistical significance was set at $p < 0.05$.

Results

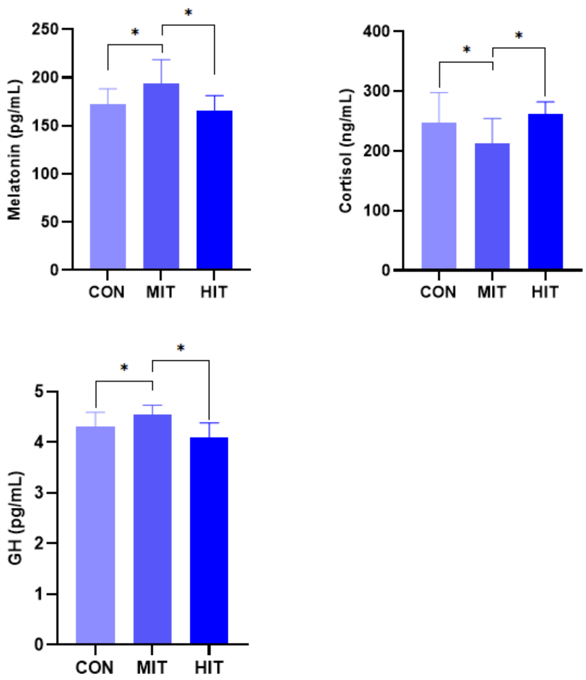
The results of the average body weight analysis before and after MIT and HIT interventions are presented in Table 2. Table 2 shows that the mean delta in body weight of the control group (CON) was higher compared to the MIT and HIT groups. Based on the results of the one-way ANOVA test, there was a significant difference in the mean delta of body weight among the groups before and after the MIT and HIT interventions ($p = 0.002$). Tukey's HSD post hoc test showed a significant difference in the mean delta of body weight between CON and HIT ($p < 0.001$), and between MIT and HIT ($p = 0.017$), while no significant difference was observed between the CON and MIT groups (p = 0.147). The results of the analysis of GH, melatonin, and cortisol levels after MIT and HIT interventions are presented in Figure 1.

Table 2. Differences in average body weight before and after MIT and HIT interventions

Group	n	Pretest mean±SD (gr)	Posttest mean±SD (gr)	Δ mean±SD (gr)	p-value
CON	13	169.38±7.32	398.62±43.97	229.23±46.38[a]	
MIT	13	169.15±7.35	373.00±42.70	203.85±43.35[a]	0.002
HIT	13	169.15±7.31	329.69±45.38	160.54±46.75[b]	

Different superscript shows significant differences in the Tukey's HSD post hoc test (p < 0.01). CON: Control group; MIT: Moderate-intensity training group; HIT: High-intensity training group.

Figure 1. Observation of GH, Melatonin, and Cortisol Levels in the Three Groups



*Significant at CON and HIT (p < 0.05).

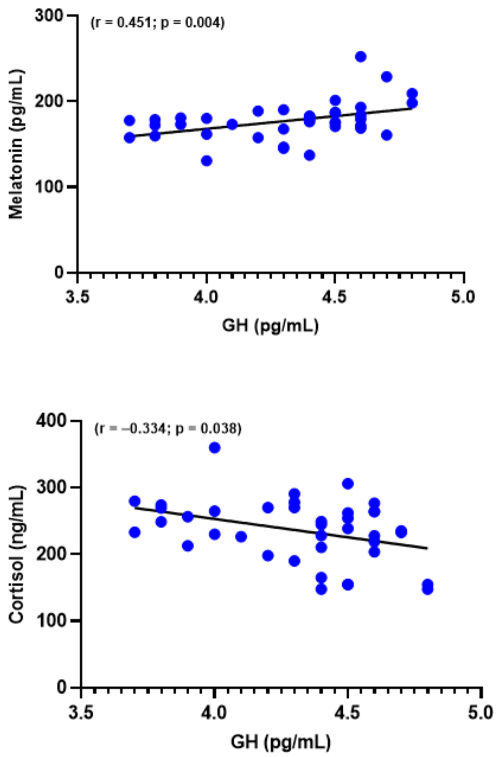
All data are presented as mean ± standard deviation (SD).

The p-value was obtained using the one-way ANOVA test and followed by Tukey's HSD post-hoc test.

CON: Control group; MIT: Moderate-intensity training group; HIT: High-intensity training group.

We observed that serum GH levels in the MIT group were higher compared to those in the HIT and CON groups (Figure 1). The one-way ANOVA test showed a significant difference in mean GH levels between groups (p < 0.001). Tukey's HSD post hoc test revealed significant differences in mean GH levels between MIT and HIT (p < 0.001), and between MIT and CON (p = 0.042), while no significant difference was found between CON and HIT (p > 0.05). We also observed that melatonin levels in the MIT group were higher compared to the HIT and CON groups. The one-way ANOVA test showed a significant difference in mean melatonin levels (p = 0.002). Tukey's HSD post hoc test showed significant differences in mean melatonin levels between MIT and HIT (p = 0.002), and between MIT and CON (p = 0.021), whereas no significant difference was found between HIT and CON (p > 0.05). The average cortisol level in the HIT group was found to be higher than that in the CON and MIT groups. The one-way ANOVA test showed a significant difference in mean cortisol levels (p = 0.019). Tukey's HSD post hoc test showed significant differences in mean cortisol levels between MIT and HIT (p = 0.017), and between MIT and CON (p = 0.046), while no significant difference was found between HIT and CON (p = 0.644). The correlation analysis among the variables is presented in Figure 2.

Figure 2. Pearson's correlation coefficient at serum growth hormone levels with cortisol and melatonin



*Significant with p < 0.05 by Pearson's correlation coefficient.

Discussion

This study examined the hormonal responses to two different exercise intensities, namely moderate-intensity training (MIT) and high-intensity training (HIT), using an animal model. The main findings showed that MIT had a more favorable effect on increasing growth hormone (GH) and melatonin levels, whereas HIT triggered a significant increase in cortisol levels. This pattern indicates that moderate-intensity exercise better supports the creation of a balanced and adaptive hormonal environment. This study also serves as a pioneering effort in integrating the measurement of these three hormones simultaneously within a single controlled experimental protocol, offering a new approach in building a systemic biomarker framework for training adaptation. This framework is relevant for understanding physiological responses to exercise, not only from a single perspective but from the overall hormonal dynamics involving anabolic, circadian, and metabolic stress processes (Hacker et al., 2023; Celorrio San Miguel et al., 2024).

Interestingly, the control group exhibited a significantly higher body weight compared to both exercise groups. This outcome aligns with previous evidence showing that physical training, particularly aerobic exercise, limits fat accumulation and modulates metabolic pathways (Zhang et al., 2024). Rats in the MIT and HIT groups likely experienced increased energy expenditure, improved mitochondrial efficiency, and elevated lipolysis. Additionally, the elevated cortisol levels observed in the HIT group may have promoted muscle protein breakdown and inhibited weight gain through catabolic activity (Dharmasanti et al., 2024). These mechanisms together contribute to the reduced weight observed in trained animals compared to sedentary controls.

The significant increase in GH levels in the MIT group is consistent with the physiological principle that moderate-intensity exercise effectively stimulates the hypothalamic-pituitary axis responsible for pulsatile GH release. This finding is supported by Kim et al. (2024), who showed that four weeks of moderate training significantly increased GH levels in obese individuals. This response reflects the potential of moderate training to induce anabolic adaptation without causing excessive physiological stress. Meanwhile, melatonin also increased significantly in the MIT group, which aligns with its role in regulating circadian rhythms and supporting tissue regeneration during rest phases. A study by Celorrio

San Miguel et al. (2024) reported that melatonin functions not only as an indicator of biological rhythms but also contributes to athletic performance by enhancing metabolic recovery and improving sleep efficiency. Furthermore, Faria et al. (2022) found that melatonin can enhance mitochondrial biogenesis in muscles and accelerate energy recovery through glycogen optimization, which serves as a foundation for long-term metabolic adaptation to training.

In contrast, the significant increase in cortisol levels in the HIT group indicates a higher degree of physiological stress. Cortisol, the primary stress hormone released through activation of the HPA axis, plays a critical role in short-term energy mobilization and metabolic homeostasis. However, elevated cortisol levels over a prolonged period can have catabolic effects and inhibit tissue growth. Caplin et al. (2021) demonstrated that high-intensity exercise, especially under psychosocial stress, consistently raises post-exercise cortisol levels. This finding is supported by Taha and Mounir (2019), who reported that high-intensity resistance training in the elderly triggered higher cortisol spikes compared to low-intensity training. Nonetheless, some controversy remains, particularly referring to the classical study by Raastad et al. (2000), which found no significant differences in GH levels between high- and moderate-intensity resistance training, despite consistent increases in cortisol. This discrepancy is most likely due to differences in exercise type (resistance in Raastad's study vs. aerobic in the current study), observation duration (acute vs. chronic), and subject population (humans vs. animal models). Using a mid-term training protocol over 12 weeks, the present study demonstrated that MIT yields a more stable hormonal balance and supports adaptive processes more effectively than HIT.

From a physiological standpoint, the hormonal mechanisms involved reflect systemic adaptation pathways to exercise loads. GH plays a central role in stimulating protein synthesis and muscle hypertrophy via hepatic production of IGF-1, which activates the PI3K/Akt/mTOR pathway and supports post-exercise muscle remodeling (Yoshida & Delafontaine, 2020). Melatonin also enhances mitochondrial biogenesis by upregulating PGC-1α and increases cellular resilience through its antioxidant actions, including the activation of enzymes such as SOD and GPx (Dhia et al., 2022; Faria et al., 2022). While cortisol is necessary for energy mobilization during stress, persistently elevated levels can inhibit muscle protein synthesis and accelerate tissue degradation (Kraemer & Ratamess, 2005). Therefore, the hormonal profile found in the MIT group—elevated GH and melatonin with moderated cortisol—reflects an optimally adaptive physiological response.

Scientifically, this study offers a meaningful contribution through an integrative approach that simultaneously measures the three key hormones. The combination of GH, melatonin, and cortisol provides a systemic overview of how the body adapts to training in terms of growth, recovery, and metabolic stress. This may serve as a foundation for developing a systemic biomarker framework for training adaptation that is not only relevant for experimental studies but also applicable in coaching and medical practices (Hacker et al., 2023).

Practically, the findings support the application of moderate-intensity exercise as an effective strategy for enhancing physiological resilience and minimizing the risk of overtraining. Given its favorable hormonal impact, MIT may be particularly beneficial for populations such as athletes, recovering patients, and individuals seeking long-term health benefits. The combined use of GH, melatonin, and cortisol as a hormonal panel may further aid in tailoring training variables to individual needs, improving both effectiveness and safety (Soler-López et al., 2024).

Although the use of rat models enables precise control over experimental conditions, caution must be exercised when extrapolating these findings to humans. Rodents and humans differ in circadian regulation, metabolic rate, and stress hormone dominance (i.e., corticosterone vs. cortisol), which may influence the endocrine responses to training (Schroeder et al., 2012). Therefore, while the present study provides important mechanistic insights, future human studies are essential to confirm the clinical relevance of these findings.

This study has several limitations that should be noted. Hormonal measurements were limited to systemic levels and thus could not directly reveal molecular outcomes or structural adaptations in muscle tissue. Downstream parameters such as IGF-1 levels, GLUT-4 expression, and muscle protein synthesis (e.g., mTOR or S6K1) were not evaluated. A study by Fujita et al. (2007) showed that phosphorylation of S6K1, as an indicator of protein synthesis, increased after low-intensity training combined with blood flow restriction. Therefore, further studies are strongly recommended to integrate both systemic and molecular biomarkers to obtain a comprehensive picture of training adaptations and to evaluate the relationship between hormonal profiles and physical performance or muscle recovery in a longitudinal manner. With such an approach, the systemic biomarker framework for training adaptation proposed in this study could evolve into an evidence-based training monitoring tool with broad applicability. Moreover, differences in species-specific stress physiology, such as the dominance of corticosterone in rodents versus cortisol in humans, as well as variations in circadian rhythms, must be considered when translating findings to human populations. Furthermore, external validity may be limited due to the controlled laboratory environment, which does not account for behavioral, psychological, or environmental factors affecting exercise adaptation in real-world human contexts.

Conclusions

Based on the results of this study, it can be concluded that moderate-intensity training, performed for 30 minutes, three times per week over 12 weeks, has a positive impact on growth-related indicators compared to high-intensity training and the control group. Therefore, future studies are recommended to re-evaluate these findings by including additional parameters, such as muscle protein levels, insulin, blood glucose, insulin-like growth factor-1 (IGF-1), and somatostatin, to further validate the results of this study.

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