SATELLITE CELL ACTIVATION AND SIGNALING PATHWAY RESPONSE IN JOINT EXERCISE ATHLETES

ATIVAÇÃO DE CÉLULAS SATÉLITES E RESPOSTA NA VIA DE SINALIZAÇÃO NOS EXERCÍCIOS ARTICULARES DOS ATLETAS

ACTIVACIÓN DE LAS CÉLULAS SATÉLITE Y RESPUESTA DE LA VÍA DE SEÑALIZACIÓN EN LOS EJERCICIOS ARTICULARES DE LOS ATLETAS

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Lu Liu[1]
(Physical Education Professional)

1. Xi'an Polytechnic University, Xi'an, Shaanxi, China.

Correspondence:
Lu Liu
Xi'an, Shaanxi, China. 710000.
LuLiu5@126.com

ABSTRACT

Introduction: Skeletal muscle satellite cells are considered the unique source of stem cells for myogenic differentiation of adult skeletal muscle cells. Upon stimulation, the skeletal muscle satellite cell can be activated through specific signaling pathways, proliferate and differentiate into a muscle cell. An analysis of the effects of key signaling pathways could provide the basis for an in-depth study of skeletal muscle formation in athletes and muscle development. Objective: This paper analyzes the effects of key signaling pathways on skeletal muscle satellite cell proliferation and differentiation. Methods: We divided 32 athletes into four groups: control, stretching, experimental, and mixed groups. The control group received no training at all, the stretching group and the experimental group received stretching training on the right gastrocnemius. The mixed group also got weight climbing training in the stretching training, initial load 30% of the athlete's weight, increasing 25% each week until 100% of body weight, at the frequency of 3 times a week. After training, gene expression of live satellite cells was measured by intramuscular signaling. Results: The FGM level of the antagonistic group (3.56±0.21) was higher than in the control group (3.25±0.18). The gene expression of HGF mRNA was higher in the mixed group (2.16±0.24) followed by the antagonistic group (2.02±0.15), the stretching group (1.81±0.25), and the control group (1.03±0.06). Conclusion: Both stretching and antagonistic training can increase gene expression in signaling pathways. Antagonistic training significantly increased the expression of HGF, MGF, and mRNA. This activity can promote muscle bulking and skeletal muscle enlargements. ***Evidence Level II; Therapeutic Studies - Investigating the result.***

Keywords: Skeletal Muscle Satellite Cells; Gene Expressions; Skeletal Muscle Enlargements.

RESUMO

Introdução: As células satélites musculares esqueléticas são consideradas a única fonte de células-tronco para a diferenciação miogênica das células musculares esqueléticas adultas. Após a estimulação, a célula satélite muscular esquelética pode ser ativada através de vias de sinalização específicas, proliferar e diferenciar-se em célula muscular. Uma análise sobre os efeitos das principais vias de sinalização poderia estabelecer as bases para um estudo aprofundado da formação muscular esquelética nos atletas e do desenvolvimento muscular. Objetivo: Este artigo analisa os efeitos das principais vias de sinal na proliferação e diferenciação das células satélites musculares esqueléticas. Métodos: Dividimos 32 atletas em quatro grupos. Grupos controle, alongamento, experimental e grupo misto. O grupo controle não recebeu treinamento algum, o grupo de alongamento e o grupo experimental receberam treinamento de alongamento no gastrocnêmio direito. O grupo misto também obteve treinamento de escalada com peso no treino de alongamento, carga inicial de 30% do peso do atleta, aumentando 25% em cada semana até 100% do peso corporal. Na frequência de 3 vezes por semana. Após os treinos, a expressão genética das células satélites vivas foi medida por intermédio da sinalização proveniente de coleta intramuscular. Resultados: O nível de MGF do grupo antagônico (3.56±0.21) foi maior que no grupo controle (3.25±0.18). A expressão gênica do mRNA HGF foi maior no grupo misto (2.16±0.24) seguido pelo antagônico (2.02±0.15), o grupo de alongamento (1.81±0.25) e o grupo controle (1.03±0.06) Conclusão: Tanto o treinamento de alongamento quanto o treinamento antagônico podem aumentar a expressão genética nas vias de sinalização. O treinamento antagônico aumentou significativamente a expressão de HGF, MGF e mRNA. Essa atividade pode promover volume e hipertrofia muscular. ***Nível de evidência II; Estudos terapêuticos - investigação dos resultados do tratamento.***

Descritores: *Células Satélites de Músculo Esquelético; Expressão Gênica; Hipertrofia do Músculo Esquelético.*

RESUMEN

Introducción: Las células satélite del músculo esquelético se consideran la única fuente de células madre para la diferenciación miogénica de las células musculares esqueléticas adultas. Tras la estimulación, la célula satélite del músculo esquelético puede activarse a través de vías de señalización específicas, proliferar y diferenciarse en una célula muscular. Un análisis sobre los efectos de las vías de señalización clave podría sentar las bases para un estudio en profundidad de la formación del músculo esquelético en los atletas y del desarrollo muscular. Objetivo: Este trabajo examina los efectos de las vías de señalización clave en la proliferación y diferenciación de las células

satélite del músculo esquelético. Métodos: Dividimos a 32 atletas en cuatro grupos. Grupos de control, de estiramiento, experimentales y mixtos. El grupo de control no recibió ningún entrenamiento, el grupo de estiramiento y el grupo experimental recibieron un entrenamiento de estiramiento en el gastrocnemio derecho. El grupo mixto también recibió entrenamiento de escalada con pesas en el entrenamiento de estiramiento, con una carga inicial del 30% del peso del atleta, aumentando un 25% cada semana hasta el 100% del peso corporal. Con una frecuencia de 3 veces por semana. Tras el entrenamiento, se midió la expresión génica de las células satélite vivas mediante la señalización de la recogida intramuscular. Resultados: El nivel de FGM del grupo antagonista (3,56±0,21) fue mayor que en el grupo de control (3,25±0,18). La expresión génica del ARNm del HGF fue mayor en el grupo mixto (2,16±0,24), seguido del grupo antagonista (2,02±0,15), el grupo de estiramiento (1,81±0,25) y el grupo de control (1,03±0,06) Conclusión: Tanto el entrenamiento de estiramiento como el antagonista pueden aumentar la expresión génica en las vías de señalización. El entrenamiento antagónico aumentó significativamente la expresión de HGF, MGF y mRNA. Esta actividad puede promover el aumento de volumen muscular y la hipertrofia. ***Nivel de evidencia II; Estudios terapéuticos - Investigación de resultados.***

Descriptores: *Células Satélite del Músculo Esquelético; Expresión Génica; Hipertrofia del Músculo Esquelético.*

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INTRODUCTION

Muscle satellite cells (SC) are undifferentiated myoblasts that exist between the muscle membrane and basement membrane. It is closely related to the repair and regeneration of damaged muscle fibers. Usually, muscle satellite cells are resting. Satellite cells can be activated to enter the cell division cycle when stimulated by the outside to achieve the repair, hypertrophy, or regeneration of muscle fibers.[1] The number of satellite cells activated is closely related to muscle hypertrophy or the speed of damage repair. Studies have confirmed that key regulatory factors such as hepatocyte growth factor (HGF) and mechanical growth factor (MGF) play an important regulatory role in the activation and proliferation of satellite cells. It is generally believed that antagonistic training can effectively activate satellite cells in skeletal muscle, which has significant significance in maintaining the number of skeletal muscle satellite cell pools and promoting skeletal muscle hypertrophy. In this study, athletes were trained in two ways: load-bearing ladders and stretching. We compared the content of HGF and MGF in gastrocnemius muscle and their gene expression.[2] In this way, we will explore effective ways to promote the activation and proliferation of satellite cells. This provides a basis for formulating rehabilitation training programs for athletes to maintain their muscle state during rest periods, patients with long-term bed rest, and senile muscular atrophy.

METHOD

General information

We randomly divided 32 athletes into a control group (N group), a stretching group (S group), an antagonistic group (R group), and a combined group (C group). We performed manual stretching training on the gastrocnemius of the right hind leg in the S group.[3]

Antagonism and stretching training program

The antagonistic training was carried out by using the tail-loaded climbing ladder method. The initial load is 30% of the athlete's body weight, and after that, it is increased by 25% every week until 100% of the body weight. The weight is maintained until the end of the training.[4] Antagonistic training trains 3 days a week.

Multi-scale mathematical models in biological systems

The chemical master equation is another way to represent a random chemical reaction system. For example, for a total of $N+1$ molecules in the reaction, there are correspondingly $0, 1, \mathrm{L}, N$ protein B molecules and $N, N-1, \mathrm{L}, 0$ protein A molecules.[5] Assuming that the probability of n B molecules at time t is $P(n, t)$, the rate of change of this probability is composed of four transitions in the corresponding state. Thus we have $N+1$ ordinary differential equations:

$$\frac{dP(n,t)}{dt} = \alpha(N-n+1)P(n-1,t) + \beta(n+1)P(n+1,t) - \beta nP(n,t) - \alpha(N-n)P(n,t) \quad (1)$$

Here $n = 0, 1, \cdots, N$. Starting from the initial distribution $P(n, 0) n = 0, 1, \cdots, N$, the corresponding probability distribution $P(n, t)$ can be obtained by solving the above-mentioned ordinary differential equations.

When the number of molecules is quite large, the main chemical equation can be approximated to Langevin's equation.[6] This is a stochastic differential equation. The Langevin equation was originally used to describe the Brownian motion of particles. Its general form is

$$dX = f(X,t)dt + g(X,t)dW \quad (2)$$

Here X is a random variable representing the number of particles. The first term at the right end of the equation is the drift term, and the second is the diffusion term. W is the Wiener process.

Statistical analysis

All results of this study were processed with SPSS18.0. Values are expressed as mean ± standard deviation. One-way analysis of variance was used for comparison between groups. The significance level is $P<0.05$, and the very significant level is $P<0.01$.

RESULTS

Comparison of MGF and HGF levels in gastrocnemius muscles of each group after the experiment

We can get Table 1 after measuring the levels of MGF and HGF in each group of samples. It can be seen that the MGF level of the training group was significantly higher than that of the control group. Compared with

Table 1. Comparison of HGF and MGF levels of the gastrocnemius muscle in each group.

	HGF	MGF
C	2.87±0.44	3.25±0.18
S	4.18±0.25	3.42±0.34*
R	4.62±0.36	3.56±0.21
M	4.76±0.73	3.64±0.26

the N group, there is a significant difference in the S group, and there is a very significant difference between the R and the C groups. Compared with the S group, there is a very significant difference between the R group and the C group, but there is no significant difference between the R group and the C group.[7]

Comparison of the expression levels of MGF, HGF, IGF-IEa mRNA in gastrocnemius muscle of each group

We can get Table 2 after measuring MGF and HGF mRNA in each group of samples. The expression level of MGF mRNA in the S, R and C groups was higher than that of the N group, and the difference was very significant. Among them, the R group has the highest average level. The expression level of HGF mRNA in the S, R and C groups was higher than that of the N group, and the difference was very significant. Group C has the highest average level, group R is higher than group S, and the difference between groups is very significant.[8] There is a significant difference between the C and R, and S groups, but the difference between the M and S groups is not obvious.

Table 2. Comparison of HGF mRNA and MGF mRNA expression levels in gastrocnemius muscle of each group.

	HGF mRNA	MGF mRNA
C	1.03±0.06	0.28±0.06
S	1.81±0.25	1.16±0.14
R	2.02±0.15	1.42±0.23
M	2.16±0.24	1.47±0.18

DISCUSSION

The expression of HGF can be detected in the early stages of muscle development and regeneration. When satellite cells or skeletal muscles are mechanically stretched, HGF will be quickly released from its storage site. At the same time, it binds to the HGF receptor (c-met) on the surface of satellite cells to activate satellite cells.[9] Mechanical growth factor (MGF) is a local autocrine growth factor that is sensitive to mechanical stretching. When expressed under mechanical stimulation and tissue damage, it activates satellite cells and increases the proliferation ability of myoblasts. It can be seen that the expression levels of HGF, MGF, and their mRNA also reflect the activation and proliferation of skeletal muscle satellite cells to a certain extent.

Many studies believe that exercise training could increase the expression of HGF, MGF, and their genes in local muscle tissues and promote the proliferation and differentiation of muscle satellite cells. However, the relationship between exercise intensity and form and the activation of muscle satellite cells has not yet been fully clarified. Some scholars have found that weight-bearing swimming training in rats can significantly up-regulate the expression of skeletal muscle MGF mRNA and promote skeletal muscle hypertrophy, but the load used is relatively small. Some scholars have observed in experiments that moderate-intensity downhill running gradually increases and the HGF content in the muscle tissue of rats continues to increase 48h after exhaustive exercise. They believe that eccentric exercise can significantly increase the expression of HGF in muscle tissue, which has a significant promotion effect on the repair and hypertrophy of muscle tissue. Some scholars have observed that the expression of MGF in the gastrocnemius muscle of rats increases significantly after exhaustive exercise and reaches a peak at 24h. They believe that heavy-duty training up-regulates the expression of MGF and is closely related to the repair of skeletal muscle damage. These research results show that exercise training effectively activates muscle satellite cells, but there is no horizontal comparison in exercise intensity and mode. In this study, the wet weight of the gastrocnemius in the R group and C group was the largest. Still, the increase in the proportion of body weight was not obvious.[10] The results of R group antagonistic strength training in this study are similar to related studies. Antagonistic training significantly increased the expression of HGF, MGF, and mRNA ($P<0.01$). And it can promote muscle hypertrophy and muscle weight.

On the other hand, some studies have observed that for mechanical stimulation of skeletal muscle, the centrifugal method is more conducive to activating muscle satellite cells than the centripetal method. Some scholars performed concentric contraction training and eccentric contraction training on the research subjects' left and right lateral femoral muscles. The results showed that compared with concentric contraction training, type IIa muscle fibers increased significantly after eccentric contraction training, and HGF mRNA was significantly up-regulated. In addition, some scholars have observed that both repeated stretching. And continuous stretching can promote the hypertrophy of the gastrocnemius muscle in the experiment. Among them, repetitive stretching is more significant. This suggests that the activation of muscle satellite cells by mechanical stimulation may mainly act on the elongation process of muscles, but they did not compare stretching and active contraction. In this study, the stretching and negative contraction training results are shown in Table 1 and Table 2. After simple stretching training, the weight of the athlete's gastrocnemius muscle increased significantly, and the expression of HGF, MGF, and its mRNA in muscle tissue also increased significantly. But the rate of increase is slightly lower than that of antagonistic strength training. The expressions of HGF, MGF, and their mRNA in the muscle tissue of the stretching and antagonistic mixed training group increased most significantly. Its amplitude even exceeds that of pure antagonistic training. It can be seen that stretching exercises can increase the replication of HGF and MGF by up-regulating the expression of HGF and MGF mRNA and then activate muscle satellite cells and can be superimposed with antagonistic strength training. But what is interesting is that the up-regulation of HGF mRNA expression in group C was not significantly different than that in group S. The reason needs further study. In addition, it was also found that the MGF of menopausal women did not change significantly after stretching exercises. But this may also be related to the study object and the way of stretching and the dose. It can be inferred that stretching training can also promote the activation and proliferation of muscle satellite cells, and the effect is better when used in conjunction with antagonistic training. However, the intensity, amplitude, and frequency used in stretching may have large individual differences for different objects. The relationship between them needs further research.

CONCLUSION

Stretching and antagonistic training can effectively up-regulate the expression of HGF, MGF, and their mRNA and activate muscle satellite cells to enter the cell cycle to divide and proliferate. The effects of stretching training and antagonistic training on satellite cell activation can be superimposed. This indicates that patients who cannot perform autonomous antagonism training can use stretching methods to help maintain and recover their muscle state.

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