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EFFECT OF EXERCISE ON TRPV1 EXPRESSION IN THE MUSCLE OF GALUR WISTAR RATS

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ABSTRACT

Background: Exercise is an activity that induces acid generation as one of the TRPV1 stimulants. Activation of TRPV1, a pain receptor, by acid, can lead to the formation of neuropeptides such as substance P and calcitonin gene-related peptides as a cause of inflammation and pain. However, chronic TRPV1 activation triggered by exercise can cause TRPV1 desensitization. **Objective:** Aim of this study was to examine the effect of different intensity exercise on TRPV1 mRNA expression in gastrocnemius muscle. **Methods:** This study was experimental study using animals models. Rats aged 12-24 weeks were given exercise interventions, a treadmill protocol, 5 times a week (30 min/day) with low (10 m/s), moderate (20 m/s), and high (30 m/s) intensity for 8 weeks. After exercise period, gastrocnemius muscle were isolated and subjected for TRPV1 mRNA expression analysis using semi quantitative real time PCR. **Results:** There was no changes of TRPV1 mRNA gene expression in gastrocnemius after treatment of different intensity exercise (p =0.694). **Conclusion:** As the conclusion, 8 weeks different intensity of exercise did not alter TRPV1 expression in gastrocnemius.

INTRODUCTION

Chronic pain is one of the main reasons adults seek health care. [1] One way that can be done to inhibit pain is to desensitize Transient Receptor Potential Vanilloid 1 (TRPV1) which is a pain receptor that is widely found in the sarcoplasmic reticulum of skeletal muscle as a receptor involved in somatic and visceral peripheral inflammation, modulation of nociceptive neuron delivery to the central nervous system, and integration of various pain stimuli. [2,3]

Exercise is an activity that induces acid generation as one of the TRPV1 stimulants. [4] Exercise can lead to the accumulation of lactic acid, which is a source of hydrogen ions, contributing to acidosis in muscles during high-intensity or prolonged anaerobic activities. [5,6] Activation of TRPV1 by acid can lead to the formation of neuropeptides such as substance P and calcitonin gene-related peptide as a cause of inflammation and pain. [7] However, chronic TRPV1 activation triggered by exercise can cause TRPV1 desensitization, so that the sensitivity of nociceptive neurons is reduced because substance P is used up and the formation of pain will be inhibited. [8–10] The Centers of Disease Control (CDC) recommends 150 minutes of moderate-intensity physical activity per week for health benefits. Bruehl et al. found that aerobic treadmill 30 min per day, 3 times per weeks for 6 weeks could decrease the pain intensity.[11] In contrast, another study by Vaegter (2016) presented that there was increase in high and low pain threshold after long term exercise. Until now, the effect of exercise on pain modulation remains controversies. [12,13] Thus, aims of this study was to find the optimum exercise intensity to modulate pain receptor (TRPV1).

In this study, rats were given exercise interventions with low, moderate, and high intensity for 12 weeks. The variable used was TRPV1 expression in the gastrocnemius muscle in Wistar rats where TRPV1 has an association with pain. The purpose of this study was to analyze the differences in the effect of low, moderate, and high exercise intensity on TRPV1 expression in the gastrocnemius

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muscle in Wistar rats. This study is expected to provide new insights into the potential of exercise as a development of therapeutic approaches for chronic pain.

MATERIALS AND METHODS

Animals and Treatment

This study is a quantitative study that used the gastrocnemius muscle tissue of Wistar rats (Rattus norvegicus) aged 12-24 weeks. The study subjects were divided into four groups: the control group with no exercise intervention (CD), exercise group with low intensity (LI), moderate intensity (MI), and high intensity (HI). The rate of each group was different, that are 10 m/s for the low-intensity group, 20 m/s for the moderate-intensity group, and 30 m/s for the high-intensity group. This rate variation was based on the lactate threshold. The rats were treated with exercise intervention 5 times a week with a duration of 30 minutes per day. This exercise treatment was carried out within 8 weeks. This study used 5 samples per group, so the total sample was 20 samples. This study was done in Animal Research Centre Universitas Padjadjaran and Central Laboratorium Universitas Padjadjaran in January to July 2024.

During the exercise intervention, the rats were provided with food and water via *ad libitum*. After 12 weeks of exercise intervention, all experimental rat groups were terminated by administering 5% isoflurane inhalation anesthesia, followed by lower limb dislocation performed by a trained individual. The muscle tissues were then extracted, cleaned from surrounding tissues, and stored in a -80°C freezer.

mRNA Extraction and Semi-Quantitative PCR

The gastrocnemius muscle tissue used from each sample was approximately 17-20 mg. Muscle tissue samples were put into a 1.5 mL microtube, and then reduced in size using a nail nipper. A total of 200 µL of GENEzol reagent (Geneaid, Biotech Ltd., New Taipei, Taiwan) was added to the microtube. The muscle sample was homogenized using a stirrer homogenizer for 45-60 seconds (5,000 - 20,000 rpm), then incubated for 5 minutes at room temperature. A total of 40 µL chloroform was added to the microtube containing the sample and homogenized again using a vortex, then incubated for 3 minutes at room temperature.

Following the incubation process, the sample was centrifuged at 11,200 rpm/12,000 xg for 15 minutes at 4°C. Take and transfer the upper phase containing RNA into a new microtube and add 100 µL Isopropanol, then homogenize using a vortex and incubate for 10 minutes at room temperature. The second centrifugation was performed at 11,200 rpm/12,000 xg for 10 minutes at 4°C. Remove the supernatant, leaving only the RNA pellet in the microtube, and add 200 µL of 70% ethanol into the tube to wash the RNA pellet, then homogenize with a vortex. The third centrifugation was performed at 11,200 rpm/12,000 xg for 5 min at 4°C. Remove the supernatant using a micropipette and leave the RNA pellet in the tube. Dry the RNA pellet for 5-10 minutes at room temperature. Add 20 µL nuclease-free water (NFW) to resuspend the RNA pellet, then incubate the sample for 10 minutes at 60°C to dissolve the RNA pellet using a heating block.

Samples were quantified to determine RNA concentration using a multimode microplate reader at 260/280 nm absorbance spectrophotometry (M200 Po, Tecan, Morrisville, NC). Measurement of mRNA expression was carried out by conventional PCR techniques and using a Sensoquest gradient PCR machine with samples, NFW, and One-Step PCR Kit as the main ingredients. GAPDH was used for each sample as an internal control and normalization. The PCR procedure was followed by electrophoresis and gel visualization using BluPAD Dual LED Blue/White Light Transilluminator (Bio-Helix Co., Taiwan). The PCR band density was quantified using ImageG software (National Institutes of Health, Wayne Rasband, USA). The mRNA expression was calculated by normalized the TRPV1 expression with GAPDH expression.

Statistical Analysis

Statistical analysis of this study was conducted using IBM SPSS V.29. Data analysis begins with a normality test using the Saphiro-Wilk test. The data is normally distributed if $p > 0.05$. Data analysis continued with a homogeneity test using the Levene test with the results of $p > 0.05$ if the data was homogeneous. To determine whether there are significant differences between treatment groups, one way ANOVA test was conducted, which indicated mean ± minimum standard error (SEM), and

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continued with Tukey HSD with a significance value of $p < 0.05$.

RESULTS

Total 20 rats were subjected to this experiment. Rats body weight were measured by the end of experiment periods (Figure 1). There was no significant difference among the groups (p=0,55).

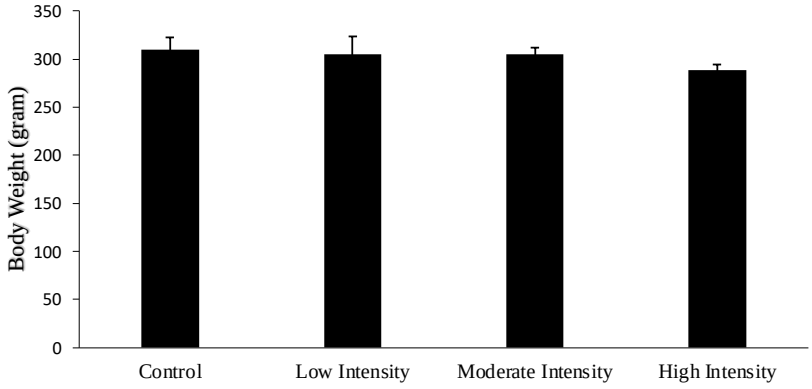

Figure 1. Body weight of rats after training periods (gram). Data was presented as Mean±SEM.

After being given various treatments, TRPV1 mRNA expression in the gastrocnemius muscle in each treatment group was observed. The value expression of TRPV1 normalized with GAPDH expressed as Mean ± SEM in the control group was 0.915 ± 0.180, the low-intensity exercise group was 0.971 ± 0.051, the moderate-intensity exercise group was 1.083 ± 0.059, and the high-intensity exercise group was 1.284 ± 0.230. The mRNA expression of TRPV1 that was normalized by GAPDH can be seen in Figure 2A and the value among the treatment groups is illustrated in Figure 2B From the results we can conclude that the high-intensity exercise group has the highest value of TRPV1 mRNA expression.

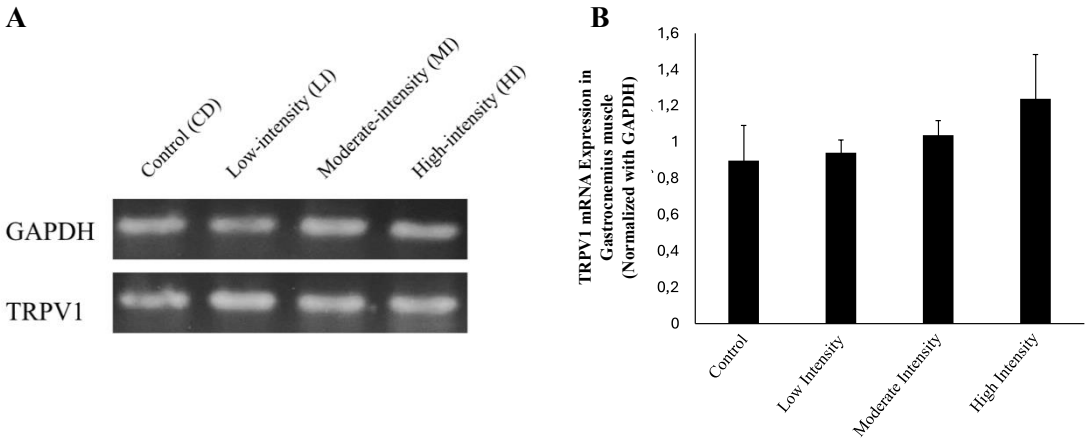

Figure 2. TRPV1 mRNA expression. A. mRNA expression of TRPV1 was normalized by GAPDH. B. Quantification of mRNA expression of TRPV1 Data presented as Mean±SEM.

The comparison between these 4 groups showed statistically insignificant results in TRPV1 expression (p=0.694). Thus, exercise did not increase TRPV1 expression in gastrocnemius muscle.

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DISCUSSION

Exercise for 8 weeks duration did not change the rats body weight significantly (Figure 1). These results were consistent with other study that after there was no significant changes of body weight until 8 weeks exercise.[14] However, the reduction of body weight started to be detected after 10 weeks exercise. Thus, longer exercise duration is needed to modulate the animal body weight.

Based on the results of this study (Figure 2A-B), it is known that the results showed statistically insignificant differences in all groups regarding the p-value which greater than 0.05 (p=0.694). This could happen because the materials used in this study is the gastrocnemius muscle which is a fast-twitch muscle rather than the soleus muscle categorized as a slow-twitch muscle. This point is supported by a study that showed a significant result of TRPV1 deficient effect in the slow-twitch muscle, therefore the impact of TRPV1 deficiency was more visible on slow-twitch muscles than on fast-twitch ones. [3] Slow-twitch or type I muscle fiber is the type that is best suited for prolonged contractions and endurance exercises such as long-distance running, cycling, and swimming, while the fast-twitch type or type II muscle fiber is best suited for short-duration, high-intensity activities, such as sprinting, weightlifting, and HIIT (high-intensity interval training). Slow-twitch fibers' higher oxidative metabolism, fatigue resistance, and chronic activity patterns compared to fast-twitch ones can create an environment where TRPV1 is more actively involved in pain modulation and inflammatory responses. [15]

If the sample used is gastrocnemius muscle, the exercise protocol provided can be an eccentric exercise because a study showed significant results of TRPV1 expression on downhill running protocol at a − 16° tilt and a constant speed for 90 minutes. Eccentric exercises can increase xanthine oxidase activity that leads to increased ROS production and oxidative stress because of the muscle damage that being produced. This will result in upregulation of TRPV1 synthesis and cause sensitization of pain pathways that led to delayed onset muscle damage (DOMS) due to the increased TRPV1 expression 12 hours after the treadmill protocol. [14] Significant TRPV1 expression also showed when observed at protein levels on immunoblotting. [15] Additionally, TRPA1 is more highly expressed in gastrocnemius muscle rather than TRPV1. [18]

Although the result is insignificant, it can be seen in the result that there is a tendency for TRPV1 expression to be the highest in high-intensity (HI) exercise group compared to other intensities. The high expression of TRPV1 in the high-intensity exercise compared to the low and moderate intensity is due to the accumulation of lactic acid during high-intensity exercise, which acid is one of the stimuli of TRPV1. [5] This accumulation of lactic acid leads to a phenomenon called metabolic acidosis which occurs when the muscles are unable to meet energy demands through aerobic metabolism and instead rely on anaerobic pathways such as glycolysis and the ATP-PC system. These pathways produce lactic acid and hydrogen ions (H+) as byproducts so that the body's pH levels drop significantly. [19] This can lead to a range of physiological and perceptual responses, including fatigue and muscle soreness that are in line with the responses of TRPV1 activation as a pain receptor. A previous study also found that low-intensity exercise showed no significant effects on cortisol, a stress hormone, that induced by exercise while the high-intensity was influenced. [20] The rise in cortisol levels following high-intensity exercise might contribute to an initial reduction in pain sensation due to its anti-inflammatory and metabolic effects. However, chronic elevation of cortisol can also lead to negative effects such as muscle breakdown and increased perception of pain over time due to prolonged stress responses. [21]

As a pain receptor widely found in the sarcoplasmic reticulum of skeletal muscle, TRPV1 has a close relationship with exercise. Sensitization of TRPV1 by acid produced by exercise results in Ca^{2+} influx and the release of molecules involved in modulating pain perception, such as bradykinin, calcitonin gene-related peptide (CGRP), and substance P. [7,8] As a result, there is an increase in pain perception, such as muscle fatigue. Long-term activation of TRPV1 can also lead to mitochondrial biogenesis in skeletal muscle via the Ca^{2+}-CaMKII-p38 MAPK-PGC-1α signaling axis. [3,22]

TRPV1 as one of the TRP channels isoform has a similar structure to other TRP channels which contain six transmembrane segments, N-terminus, and C-terminus. [2] To regulate TRPV1 activity, particularly to prevent excessive activation, TRPV1

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desensitization involves multiple mechanisms that work together including Ca^{2+}-dependent binding of calmodulin, ATP-mediated inhibition, and phosphorylation/dephosphorylation processes. ATP and calmodulin have the same binding sites which are located in the C-terminus. [22] ATP and calmodulin will compete for binding to the same site on TRPV1, with ATP sensitizing the channel and calmodulin inhibiting it to regulate TRPV1 activity. The presence of ATP can inhibit the binding of calmodulin, thereby reducing the inhibitory effect on TRPV1 activity. Meanwhile, calmodulin is Ca^{2+}-dependent. Ca^{2+} influx through TRPV1 channels triggers a negative feedback loop that leads to desensitization. This process involves the binding of calmodulin to TRPV1, which inhibits the channel's activity. [23,24]

Exposure to any TRPV1 stimuli will certainly activate TRPV1. However, a long-term or repeated exposure to capsaicin as the TRPV1 stimulant can cause TRPV1 desensitization so that the sensitivity of nociceptive neurons is reduced because substance P is used up and the formation of pain will be inhibited. [8,9] This desensitization theory was supported by electroacupuncture as a pain treatment that showed a significant increase in TRPV1 protein expression. [17] Several experimental and clinical studies provided evidence that capsaicin protects against ischemic or excitotoxic cerebral neuronal injury and may lower the risk of cerebral stroke. [25] Chronic exposure to low levels of capsaicin can lead to sustained desensitization of TRPV1, a receptor that is highly expressed in nociceptive neuron dorsal root ganglion, which is sometimes exploited in therapeutic settings to reduce chronic pain. [24,27] Thus, capsaicin has dual mechanisms for inducing TRPV1 where the initial activation of TRPV1 will release pro-inflammatory cytokines, contributing to pain and inflammation, while the prolonged exposure to capsaicin leads to a reduction in the release of cytokines and other neuropeptide, contributing to the analgesic effects [27] These dual mechanisms also applied to other TRPV1 stimulants, such as cannabinoid. [28] Exercise also tends to contribute as a therapeutic setting in pain management because the rise in cortisol levels following high-intensity exercise might contribute to an initial reduction in pain sensation due to its anti-inflammatory and metabolic effects. [21] However, the exercise-induced analgesic effects still need further research.

Many limitations are present in this study. First, we only examine one type of pain receptor (TRPV1). Second, only gastrocnemius muscle was used in this study. Thus, further study is needed to compare the TRPV1 expression in another type of skeletal muscle, for example soleus or thigh muscle. Another study on difference pain receptor such as ASIC should be conducted to get more comprehensive understanding about effect of exercise in pain receptor.

CONCLUSION

In conclusion, these findings showed an insignificant result of TRPV1 expression, but have a tendency that TRPV1 expression is highest in the high-intensity exercise group compared to the low and moderate-intensity exercise. These results can be used as a basis to determine which intensity of exercise can be exploited in therapeutic settings to reduce chronic pain referring to the capsaicin-induced TRPV1 desensitization theory.

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