2025, Retos, 62, 666-670

Altered extracellular ATP ADP, and amp hydrolysis in blood serum of sedentary individuals after an acute, strength, exercise session

Alteración de la hidrólisis de ATP, ADP y amp extracelular en suero sanguíneo de individuos sedentarios tras una sesión aguda de ejercicio de fuerza

*Samuel Vargas Munhoz, **Cesar Eduardo Jacintho Moritz, ***Franccesco Pinto Boeno, *Andriéli Aparecida Salbego Lançanova, *Alvaro Reischak-Oliveira, ****Roberto Rebolledo-Cobos, *****Luisa Galeano-Muñoz, *****Raúl Polo-Gallardo, ******Bruno Costa Teixeira
*Federal University of Rio Grande do Sul (Brasil), **University of Delaware (Estados Unidos), ***University of Florida (Estados Unidos), **** Universidad Metropolitana (Colombia), *****Universidad Simón Bolívar (Barranquilla, Colombia), ******State University of Minas Gerais (Brasil)

Abstract. Nucleotidases participate in the regulation of physiological and pathological events, such as inflammation and coagulation. Different types of physical exercise promote changes in purinergic signaling. In the present study, we investigated the activities of soluble nucleotidases in the blood serum of sedentary young male adults before and after a resistance exercise session. In addition, we evaluated how this type of exercise could influence the concentrations of adenine nucleotides in the blood serum. The individuals were submitted to a strength exercise session, consisting of 8 exercises. Blood samples were collected pre- and post-exercise, and serum was separated for analysis. Results showed increases in ATP, ADP, and AMP hydrolysis post-exercise, compared to pre-exercise values. Our results demonstrate that a resistance exercise session modifies ATP metabolism, being one more form of exercise that can positively influence cardiovascular and metabolic health.
Keywords: Nucleotidases, Purinergic signaling and strength exercise.

Resumen. Las nucleotidasas participan en la regulación de eventos fisiológicos y patológicos, como la inflamación y la coagulación. Diferentes tipos de ejercicio físico promueven cambios en la señalización purinérgica. En el presente estudio, investigamos las actividades de nucleotidasas solubles en el suero sanguíneo de adultos jóvenes sedentarios de sexo masculino antes y después de una sesión de ejercicio de resistencia. Además, evaluamos cómo este tipo de ejercicio podría influir en las concentraciones de nucleótidos de adenina en el suero sanguíneo. Los individuos fueron sometidos a una sesión de ejercicio de fuerza, consistente en 8 ejercicios. Se recolectaron muestras de sangre antes y después del ejercicio, y se separó el suero para su análisis. Los resultados mostraron aumentos en la hidrólisis de ATP, ADP y AMP después del ejercicio, en comparación con los valores previos al ejercicio. Nuestros resultados demuestran que una sesión de ejercicio de resistencia modifica el metabolismo del ATP, siendo una forma más de ejercicio que puede influir positivamente en la salud cardiovascular y metabólica.
Palabras clave: Nucleotidasas, Señalización purinérgica y ejercicio de fuerza.

Fecha recepción: 11-07-24. Fecha de aceptación: 22-10-24
Luisa Galeano-Muñoz
luisa.galeanom@unisimon.edu.co

Introduction

The current sedentary lifestyle has been associated with the increase in the incidence of non-transmissible chronic diseases, the World Health Organization (WHO), brings that about 70% of the world population is sedentary, that is, does not perform the minimum amount of daily physical activities [1, 2]. In contrast, it has been demonstrated that physical exercise promotes several molecular and tissue adaptations, being a non-pharmacological alternative for the treatment of chronic diseases, such as diabetes, hypertension, and cardiovascular diseases [3, 4].

Among these adaptations, it is possible to modulate nucleotides and nucleosides, known to mediate several biological functions of the body, such as inflammation, coagulation processes, fibrinolysis, and neurotransmission processes, probably involved in the pathophysiology of several diseases. [5-7].

Data published by our group demonstrate the influence of aerobic exercise on purinergic signaling. Moderate exercise increases the hydrolysis of ATP, ADP and AMP in the blood serum of young adults [8] demonstrating the interaction with the cardioprotective effect of exercise, however, to our knowledge, there are still no studies that have evaluated strength exercise and its relationships with purinergic signaling. Moderate-intensity strength exercise is also known as cardioprotective, ensuring better strength levels, more functionality and less cardiac overload. [9,10]. Some studies have shown that the increase in ATP concentration in the extracellular environment and the increase in adrenergic stimulation caused by high-intensity strength exercise can stimulate purinergic P2 receptors, which help to increase the reflex response of increased blood pressure in humans. , however these mechanisms are still not completely clear, but they raise the importance of understanding the responses of strength exercise and their different intensities on the purinergic system [11, 12].

We know that, trained participants submitted to strenuous aerobic exercise showed a temporary increase in ADPase activity in the blood serum and increase levels ATP, ADP, and AMP extracellular in the blood plasma, demonstrating the importance of intensity [8, 13]. In this context, the aim of this study is to investigate and compare ATP, ADP, AMP, and 5-NT responses after a session of traditional strength exercise in sedentary young individuals.

Materials and Methods

Participants

Eleven young adult males with a mean (±SD) age 22.2 ± 2.4 years participated in the study. The participants were sedentary, had not been engaged in any exercise program for at least 6 months, had no previous diseases, had received no pharmacological treatment for at least 60 days, and were non-smokers. Participants with a history of alcohol abuse were excluded (2 doses per day). The volunteers were instructed to abstain from caffeine for 12h before tests. Informed consent was obtained from all individual participants included in the study. The study was conducted according to the declaration of Helsinki and was approved by the Ethics Committee of the Universidade Federal do Rio Grande do Sul (protocol number 79422417.2.0000.5347) and all participants signed the informed consent form.

Experimental protocol

The experimental protocol was carried out on 2 different days in the Exercise Research Laboratory Federal University of Rio Grande do Sul (UFRGS). On the first day, all participants were interviewed and clinically evaluated. Data regarding disease history, including any chronic condition of volunteers as respiratory, cardiac, metabolic, and musculoskeletal diseases, as well as medical history of first-degree family, pharmacological treatments, diet, exercise, and alimentary habits were collected. Individuals with any previous or familial condition that could influence the results of our study were excluded. Additionally, the participants answered the Physical Activity Readiness Questionnaire (PAR-Q), used to exclude individuals with inappropriate health conditions. Body mass, height and body mass index (BMI) were measured, in addition to a 1RM test to obtain the values referring to the participants' maximum strength [14].

Muscle strength evaluation (1 RM) was realized for bench press, leg press, pulled forward, knee extension and flexion, biceps curl and triceps pulley. 1-RM test was performed using the same equipment employed for the resistance exercise sessions. To control the movement speed during the test, a Quartz metronome with a 1-Hz resolution was used. The cadence of the knee extension exercise was 2 s for the concentric phase and 2 s for the eccentric phase [15].

Seven days after evaluations, on the second day of the experimental protocol, participants arrived at the laboratory and rested for 30 min in a supine position. After rest, the pre-exercise blood samples and capillary glycemia (glucometer Accu Check Advanced, Roche, Switzerland) were collected. Participants were subjected to 8 strength exercises: Bench Press, Leg Press, Forward Pull, Knee Extension and Flexion, Biceps Curl, Triceps Pulley at 70% of their 1RM for 3 sets between 10 to 12 repetitions with 3 minutes rest per repetition.

Isolation of blood serum samples

Blood samples (10 mL) were collected before and immediately after the exercise protocol from the vein of the antecubital region. The blood was collected in plastic tubes without anticoagulant. For blood serum isolation, samples were allowed to clot at room temperature for 30 min before centrifugation at 5000 rpm for 10 min. After centrifugation, the clot was discarded, and the serum samples used for enzymatic assay. Serum aliquots were stored at -80°C for posterior analysis of blood biochemistry.

Chemicals

Nucleotides, p-nitrophenyl thymidine 50-monophosphate (p-Nph-50-TMP), adenosine (ADO), inosine (INO), coomassie brilliant blue G, tris, methanol, tetrabutylammonium hydroxide, and potassium phosphate monobasic were obtained from Sigma Chemical CO. (ST. Louis, MO, USA). The biochemical blood parameters were evaluated by commercial kits from Labtest™ diagnostic reagents (Labtest Diagnostica S/A, Minas Gerais, Brazil). All other reagents were also of analytical grade.

Protein determination

Protein was measured by the coomassie blue method, using bovine serum albumin as standard [16].

Assay of NTPDase and 5-nucleotidase activity

For the incubation of NTPDase and 50-nucleotidase in blood serum, a reaction medium containing 112.75 mM (final concentration) Tris–HCl buffer, pH 8.0 was used. Samples were pre-incubated for 10 min at 37°C and, to start the reactions, substrates (ATP, ADP, and AMP) were added to the reaction medium to a final concentration of 3 mM. At 50 min after the incubation, 5% (final concentration) trichloroacetic acid (TCA) was added to stop the reaction and the samples were subsequently chilled on ice. The samples were centrifuged for 10 min and the amount of inorganic phosphate (Pi) released was assayed by the malachite green colorimetric method with minor modifications [17]. Controls were performed to correct the non-enzymatic substrate hydrolysis by adding blood serum after

the reactions had been stopped with TCA. Incubation times and protein concentration were chosen to ensure the linearity of the reaction. All samples were processed in triplicate. Enzyme activities were expressed as nmol of Pireleased per minute per milligram of protein (nmol/min/mg).

NPP activity assay

Phosphodiesterase activity was assessed using p-Nph-50-TMP (an artificial marker substrate that is used for the in vitro assay of this activity), as previously described [18]. The NPP activity reaction was performed in a medium containing Tris–HCl at a final concentration of 112 mM, pH 8.9. Approximately 1 mg of serum protein was preincubated for 10 min at 37°C. The enzyme reaction was started by the addition of 0.5 mM (final concentration) of p-Nph-50-TMP. After 60 min of incubation, 200 lL of NaOH 0.2 N were added to the medium to stop the reaction. Incubation times and protein concentration were chosen for the linearity of the reaction. The amount of pNph-50-TMP released from the substrate was measured at 410 nm using a molar extinction coefficient of 18.8 9 10-3/M/cm. Controls to correct for non-enzymatic substrate hydrolysis were performed by adding blood serum after the reaction had been stopped with NaOH. All

samples were analyzed in triplicate. Enzyme activities were expressed as nmol of p-nitrophenol released per minute per milligram of protein (nmol/min/mg).

Statistical analysis

The Shapiro–Wilk test was used to assess the normality of data for each variable. For comparison of pre- and post-acute exercise values was made by Student's t test for paired samples. Statistical Package for Social Sciences (version 26; IBM Corp., Armonk, N.Y., USA) was utilized and probability level was determined as $p < 0.05$. Results are expressed as mean ± standard error mean (SEM).

Results

Table 1 describes the anthropometric characteristics and muscular strength of 11 participants (N=11). The mean age of the participants is 22.27 ± 2.49 years, with a body mass of 75.40 ± 10.33 kg and a height of 1.75 ± 0.05 m, resulting in a body mass index (BMI) of 24.5 ± 3.97 kg/m². Regarding the maximum strength measurements (1 RM), the following mean values and standard deviations are observed: bench press 50.72 ± 9.22 kg, leg press 198.81 ± 28.02 kg, front pull-down 48.27 ± 9.68 kg, knee extension 54.90 ± 5.76 kg, knee flexion 61.09 ± 7.10 kg, biceps curl 31.09 ± 9.75 kg, and triceps pulley 35.45 ± 9.34 kg.

Table 1.
Baseline characteristics of sedentary participants

Variables	N=11
Age (years)	22,27±2,49
Body mass (kg)	75,40±10,33
Height (m)	1,75±0,05
BMI (kg/m^2)	24,5±3,97
1 RM	
Bench Press	50,72±9,22
Leg Press	198,81±28,02
Forward Pull	48,27±9,68
Knee Extension	54,90±5,76
Knee Flexion	61,09±7,10
Biceps Curl	31,09±9,75
Triceps Pulley	35,45±9,34

Value are presented as mean ± SD. BMI: body mass index; RM: maximum repetition

ATP, ADP, and AMP (Fig. 1 a, b, c, respectively) hydrolysis was significantly higher in the blood serum of sedentary participants submitted to an acute protocol of strength exercise when compared to pre-exercise values (0,116 ± 0,028 vs 0,082 ± 0,009 p = 0,01; 0,145 ± 0,027 vs 0,094 ± 0,015 p = 0,04; 0,127 ± 0,017 vs 0,087 ± 0,007 p = 0,04 nmol Pi/min/mg protein) respectively. The activity of NPP (Fig. 1d), measured by hydrolysis of p-Nph-50-TMP, was also increased post-exercise in comparison to pre-exercise levels (6,656 ± 0,380 vs 5,406 ± 0,279 p = 0,01 nmol pnitrophenol/min/mg protein) respectively.

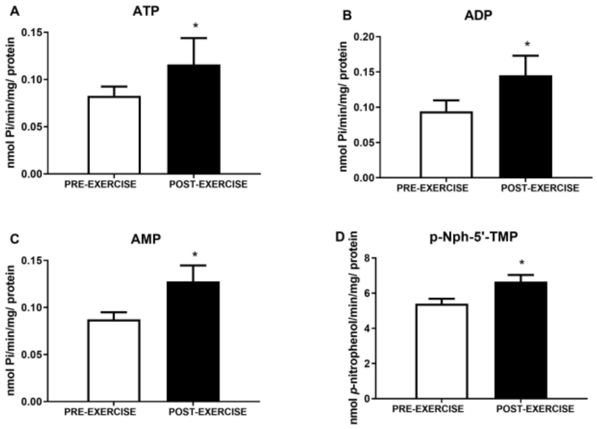

Figure 1. A: ATP, b: ADP, c: AMP, and d p-Nph-50-TMP hydrolysis in the blood serum of sedentary male individuals, pre- and post-acute session of strength exercise. Data are presented in mean ± SEM. *Indicate the difference from pre-exercise (p<0,05)

Discussion

This is the first study to investigate and compare soluble nucleotidase activity in the blood serum of sedentary young adults before and after a traditional resistance exercise session. The main finding of this study indicates in a pioneering way that a strength exercise session can alter the activity of nucleotidases in blood serum. Our results demonstrate a significant increase in ATP, ADP, AMP e *p*-Nph-5'-TMP hydrolysis, immediately after a traditional strength session. Modification of blood plasma and serum levels of nucleotides and nucleosides have already been observed in different exercise strategies, gathered in a recently published review [19] and our study adds a new possibility of intervention to modify the serum levels of nucleotidases.

In sedentary individuals, it is possible to identify a pro-inflammatory state, lower cardiorespiratory fitness, higher risk of cardiovascular diseases and metabolic syndrome [20]. In this sense, transient increases in purinergic signaling resulting from physical exercise may influence inflammatory parameters, coagulation, and vascular activity, ensuring a protective cardiometabolic effect [21]. Accordingly, Yegutkin et al., (2007); Moritz et al., (2017); Moritz et al., (2021) observed an increase in nucleotidase activities in response to different exercise protocols, applied to trained and sedentary individuals. In addition, these studies demonstrated that exercise was able to modify, at least temporarily, purine levels in plasma and blood serum [8,19,22].

Although it is not clear in the literature, repeated muscle contractions, shear stress and transient hypoxia generated by strength exercises may be a possible common way of modifying purinergic pathways [23-24]. Furthermore, it is possible that adenosine is a contributing factor to increased vasodilation during transient hypoxic exercise [24]. Moderate-intensity strength exercise induces vasodilation maintained after exercise and after training with high vasodilator factors, maintaining and improving muscle strength, providing lower cardiac overloads during activities of daily living [9,10].

Previously published by our group, a moderate-intensity aerobic exercise session increased post-exercise hydrolysis of ATP, ADP, AMP and p -Nph-5'-TMP in the serum of sedentary male participants (Moritz et al., 2017). Together with the above data, we hypothesize that different models of acute exercise lead to a transient modulation of NTPDse, 5'-NT and NPP functionality in trained and untrained individuals. These extracellular purinergic system modulations can be observed as a way of signaling for diseases and physiological alterations, as well as physical exercise monitoring strategies. [25]

Strength exercise promotes tissue and cell changes, modifying the state of body homeostasis and all responses are mediated by cell signals. In this sense, although we did not assess the concentrations of nucleotidases, it is possible to observe that the activity of nucleotidases was altered, suggesting a change in concentration. Furthermore, we suggest in future studies the analysis of the post-exercise behavior of these variables, since in a previous study of our group with aerobic exercise, the modification of the purinergic signaling is transitory. On the other hand, our study strongly controlled the exercise session and performed the 1RM of the participants for each exercise, guaranteeing the session at moderate intensity, as well as the analysis methods are robust, guaranteeing data validation and reproducibility.

Competing interests

None declared.

Author contributions

Design of the study: SVM, CEJM, ARO and BCT. Data collection, analysis and interpretation: SVM, CEJM, AASL, ARO and BCT. Draft the paper: SVM, FPB, CEJM and BCT. Critical review: SVM, CEJM, ARO and BCT. All persons designated as authors qualify for authorship and all authors have approved the final version of the manuscript.

Data Availability Statement

Data generated or analyzed during this study are provided in full within the published article.

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Datos de los/as autores/as y traductor/a:

Luisa Galeano-Muñoz	luisa.galeanom@unisimon.edu.co	Autor/a
Samuel Vargas Munhoz	samuel.munhoz9@gmail.com	Autor/a
Cesar Eduardo Jacintho Moritz	cjacinthomoritz@ufl.edu	Autor/a
Franccesco Pinto Boeno	boenofp@gmail.com	Autor/a
Andriéli Aparecida Salbego Lançanova	andrielesalbego@hotmail.com	Autor/a
Alvaro Reischak-Oliveira	alvaro.oliveira@ufrgs.br	Autor/a
Roberto Rebolledo-Cobos	rrebolledo@unimetro.edu.co	Autor/a
Raúl Polo-Gallardo	raul.pologa@unisimon.edu.co	Autor/a
Bruno Costa Teixeira	bruno.teixeira@uemg.br	Autor/a
Diana Carolina Muller	muller.dc@ufl.edu	Traductor/a