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Isometric training promotes changes in acetylcholinesterase and muscle strength
El entrenamiento isométrico promueve cambios en la acetilcolinesterasa y la fuerza muscular

*Rodrigo Rodrigues da Conceição, **Roberto Laureano-Melo, ***Cláudio da Silva Almeida, **Alba Cenélia Matos da Silva, **Anderson Luiz Bezerra da Silveira, ****Renato Vidal Linhares, **Michelle Porto Marassi, ***** Monica Akemi Sato, *Gisele Giannoco, ****Gabriel Costa e Silva, **Wellington Côrtes
*Universidade Federal de São Paulo (Brasil), **Universidade Federal Rural do Rio de Janeiro (Brasil), ***Universidade Estadual de Maringá (Brasil), **** Colégio Pedro II (Brasil), ***** Centro Universitário Faculdade de Medicina do ABC (Brasil)

Abstract. Introduction: Isometric strength training (IST) is an important component of different types of sport and others activities of daily life. However, until the present moment, no studies have linked the isometric strength training with acetylcholinesterase (AChE) activity changes. Objective: We evaluated the effects of IST on the muscular AChE activity and strength. Materials and Methods: Wistar rats (n =20) were divided into 2 groups: Control group (Ctr) (sedentary) and trained group (Tr) (submitted to 8 weeks of Isometric strength training). The muscle strength and the acetylcholinesterase activity were evaluated in the solear (SOL) and Extensor Digitorum Longus (EDL) muscles. Results: The body weight of the trained animals was 7.39 % lower than in Ctr rats ($p < 0.01$) and the EDL weight was 25 % higher ($p < 0.05$) compared to Ctr. Further, an increase of 30.36 % in strength was observed in the fourth week ($p < 0.006$) and 26.41 % in eighth week ($p < 0.003$) of training. In addition, we found an increase of 46.64% in AChE activity in the SOL. In contrast, a reduction of 55.36% in AChE activity in the EDL was observed. Conclusion: Our findings indicate that biochemical, zoometric and functional changes can be evoked by IST with low overload.
Keywords: Isometric Strength Training, Solear, Extensor Digitorum Longus and Enzyme.

Resumen. Introducción: El entrenamiento de fuerza isométrica (EFI) es un componente importante de diferentes tipos de deportes y otras actividades de la vida diaria. Sin embargo, hasta la fecha, ningún estudio ha relacionado el entrenamiento de fuerza isométrica con cambios en la actividad de la acetilcolinesterasa (AChE). Objetivo: Evaluar los efectos del EFI sobre la actividad de la AChE y la fuerza muscular. Material y Métodos: Las ratas Wistar (n =20) se dividieron en 2 grupos: Grupo Control (Ctr) (sedentario) y Grupo Entrenado (ETr) (sometido a 8 semanas de entrenamiento de fuerza isométrica). Se evaluaron la fuerza muscular y la actividad acetilcolinesterasa en el músculo soleo (SOL) y el músculo extensor largo de los dedos (ELD). Resultados: El peso corporal de los animales entrenados fue 7.39% menor ($p < 0.01$) y el peso de los ELD fue 25% mayor ($p < 0.05$) respecto a las ratas Ctr. Hubo un aumento de 30.36% de fuerza en los animales entrenados. cuarta semana ($p < 0,006$) y 26,41% en la octava semana de entrenamiento ($p < 0,003$). Además, se observó un aumento del 46,64% en la actividad de AChE en el SOL. Por el contrario, hubo una reducción del 55,36% en la actividad de la AChE en ELD. Conclusión: Nuestros hallazgos indican que el EFI con baja sobrecarga puede causar cambios bioquímicos, zoométricos y funcionales**.**
Palabras clave: Entrenamiento de Fuerza Isométrica, Soleo, Extensor Largo de los Dedos y Enzimas.

Resumo. Introdução: O treinamento de força isométrica (TFI) é um componente importante de diferentes tipos de esporte e outras atividades da vida diária. Porém, até o momento, nenhum estudo relacionou o treinamento de força isométrica com alterações na atividade da acetilcolinesterase (AChE). Objetivo: Avaliar os efeitos do TFI na atividade da AChE e força muscular. Material e Métodos: Ratos Wistar (n =20) foram divididos em 2 grupos: Grupo Controle (Ctr) (sedentário) e Grupo Treinado (Tr) (submetido a 8 semanas de treinamento de força isométrica). Foi avaliada a força muscular e atividade da acetilcolinesterase no músculo solear (SOL) e extensor longo dos dedos (ELD). Resultados: O peso corporal dos animais treinados estava 7,39% menor ($p < 0,01$) e que o peso do ELD estava 25% maior ($p < 0,05$) comparado aos ratos Ctr. Houve aumento de 30,36% de força na quarta semana ($p < 0,006$) e 26,41% na oitava semana de treinamento ($p < 0,003$). Além disso, foi observado um aumento de 46,64%, na atividade da AChE no SOL. Em contraste, houve redução de 55,36% na atividade da AChE no ELD. Conclusão: Nossos achados indicam que alterações bioquímicas, zoométricas e funcionais podem ser provocadas pelo TFI com baixa sobrecarga.
Palavras-chave: Treinamento de Força Isométrico, Solear, Extensor Longo dos Dedos e Enzima.

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Gabriel Costa e Silva
fisiologia.costaesilva@gmail.com

Introduction

Isometric strength training (IST) is an important component of different types of training activity and others activities of daily life (Lac & Cavalie, 1999; Rojas-Quinchavil et al., 2021). Despite this, little is known about the physiological effects of this type of exercise. Most studies in this direction are related to neuromuscular functional responses and morphological changes (Abe et al., 2000; Finer et al., 1994; Garfinkel & Cafarelli, 1992; Moritani & Devries, 1979), nevertheless, few studies explore biochemical changes (Tamaki et al., 1992). According to Gaspersic et al. (1999), despite acetylcholinesterase (AChE) is a key enzyme in the regulation of neuromuscular junction (NMJ) activity, there is a scarcity of information in the literature about the changes in its activity caused by IST. The cholinesterases (Cho) are a family of proteins that are widely distributed in neuronal and non-neuronal tissues classified as acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) based on their substrate specificity and inhibition (Anglister et al., 2008). AChE seems to have many more functions than BuChE. For instance, changes in levels and properties of AChE are associated with responses to numerous external stimuli (Soreq & Seidman, 2001), as well as the precise temporal control of muscle contraction that quickly eliminates the acetylcholine (ACh) action (Rosenberry, 1979). The serine hydrolase is found in the muscle, in the basal lamina at the endplate region (Anglister, 1991, Blotnick et al., 2012), indeed, most of AChE content in NMJ is produced in the muscles (Gaspersic et al., 1999). In addition, this enzyme performs essential function in cholinergic transmission, catalyzing the hydrolysis of the acetylcholine (ACh) in acetic acid and choline (Marcel et al., 1998).

Interestingly, the catalytic capacity of AChE can be related with the pattern of activation of the muscles (Gaspersic et al., 1999). In fact, denervation induces the AChE activity and expression and elicits the loss of muscle mass (Decker & Berman, 1990). In contrast, rats submitted to running can show increased AChE activity (Gorzi et al., 2013). Again, this enzymatic alteration seems to occur in parallel to zoometric changes induced by exercise as this exercise protocol can induce muscle mass gain in rats (Bonnet et al., 2007).

Currently, to the best of our knowledge, no previous study has investigated the effect of IST on the activity of acetylcholinesterase (AChE). Thus, we intended to explore the simple but seductive hypothesis: different types of muscle promote overall adaptation in the AChE activity.

Materials and methods

Animals

Twenty (n = 20) Wistar rats with 60 days of age, weighing ~220 g, supplied by Federal Rural University of Rio de Janeiro Animal Facility were used in this study. All animals were housed at controlled room temperature of 21 ± 2°C with daily exposure to 12h light-dark cycle and free access to water and standard rodent chow pellets. The animals were fed with Labina® food for rodents, which has 23% crude protein according to the label, meeting the nutritional requirements for rats according to Pastuszewska et al. (2000). This investigation was carried out according to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health 8th edition (2011) and was approved by the institutional ethics committee on animal use in consonance with pertinent Brazilian legislation (protocol number: 23083.006390/2010-34).

Table 1.
Protocol of progressive isometric strength for 8 weeks.

Time (week)	Sets	Rest (sec.)	Loading (g.)
1	5	20	35
2	5	20	40
3	6	25	40
4	6	25	45
5	7	35	50
6	7	35	50
7	8	35	55
8	8	35	60

Training Protocol

The rats were randomly divided into 2 groups: Control group (Ctr) (sedentary) and trained group (Tr) (submitted to 8 weeks of Isometric strength training). Each animal of the trained group performed isometric strength exercise, five days a week for 8 weeks, according to the model described by Lac & Cavalie (1999). As shown in table 1, the animals were submitted to a progressive training protocol in which, the series and exercise intensity were progressively increased.

Laboratory Methods

To assess muscle strength, we used the method described by Bertelli & Mira (1995). The force measurement was performed at the beginning of experimental protocol, in the fourth week and in the eighth week. Two days after the last day of training, the animals were euthanized. Afterwards, SOL and EDL were collected and weighted. Subsequently, the samples were placed in liquid nitrogen and stored in an -80 ºC ultrafreezer. Finally, to evaluate the cholinesterase activity in SOL and EDL muscles, we used the method of described by Ellman et al., 1961.

Statistical Analysis

All results are presented as means ± SEM (standard error of mean). The assumption of normal data distribution was assessed with the Shapiro-Wilk test. If the data did pass in the normality test, parametric comparisons were performed. In this case, between-group comparisons were analyzed with unpaired Student's t-test or two-way ANOVA followed by Bonferroni posttest. We performed the Pearson correlation to check the correlation between the strength and muscle weight. A Cohen's d effect size (Cohen, 1977) was carried out to show the magnitude of the differences between the groups. Differences were considered statistically significant when values $P < 0.05$. GraphPad Prism 5 statistical software (La Jolla, CA) was used for all statistical analysis.

Results

In the cholinesterase activity assay, an increase of 46.64 % in AChE activity in SOL muscle ($p = 0.01$) and a decrease of 55.36 % in the AChE activity in EDL muscle ($p = 0.01$) was observed in trained compared to control rats (figure 1).

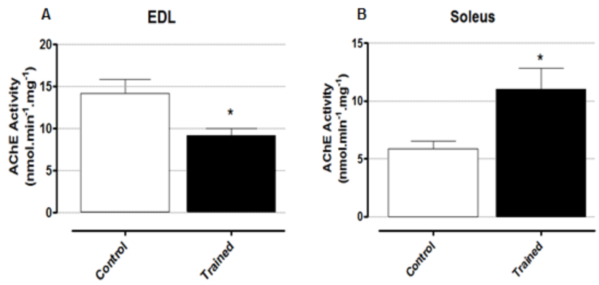

Figure 1. (A) Cholinesterase activity in EDL muscle: Control and trained group Cholinesterase activity in SOL muscle: Control and trained group. *Represent p < 0.05.

According to our results, the isometric strength training proposed by Lac & Cavalie (1999) promoted changes in zoometric and biochemical parameters. As observed in table 2, at the end of eighth week, the animals who underwent to strength training showed the body weight 7.39 % lower than Ctr rats (p < 0.01) and the relative EDL muscle weight 25 % higher than Ctr animals (p < 0.05).

Table 2.
Comparison of body weight, SOL and EDL relative weight after 8 weeks of isometric resistance training.

	Control	Trained
Body Weight (g.)	366.0 ± 18,25	340.8 ± 17.78*
SOL Relative Weight (g/BW)	0.038 ± 0.006	0.040 ± 0.005
EDL Relative Weight (g/BW)	0.051 ± 0.011	0.068 ± 0.018**

* p < 0.01 vs. control (unpaired Student´s t-test). **p < 0.05 vs. control (unpaired Student´s t-test).

However, significant differences were not observed in the SOL relative weight. Furthermore, we also found that this same kind of training caused strength gain in trained animals. Using the two-way ANOVA test, we observed a statistically significant effect of training [F (1, 54) = 13.82, p < 0.001], time [F (2, 54) = 7.47, p = 0.001] and the interaction between the experimental variables [F (2, 54) = 4.20, p = 0.02] (Figure 1). In the table 3, using two-way ANOVA followed by the Bonferroni's multiple comparisons test, it can be noted that the trained group had an increase of 30.36 % in strength in fourth week (p < 0.006) and of 26.41 % in eighth week (p < 0.003) compared to Ctr rats.

Table 3.
Strength levels values at different times.

	Control	Trained
Beginning (Before Training)	538.5 ±36.87	529.5 ± 26.01
Week 4	436.5 ± 25.07	569.0 ± 27.41**
Week 8	541.1 ± 15.42	684.0 ± 38.50*

* p < 0.01 vs. control (Two-way ANOVA). **p < 0.001 vs. control (Two-way ANOVA).

Finally, we decided to analyze whether there was a correlation between the strength and the relative weight of EDL and SOL. Thus, in figure 2, by Pearson's correlation, we verified that there was only correlation between the strength and the EDL relative weight, (p = 0.03).

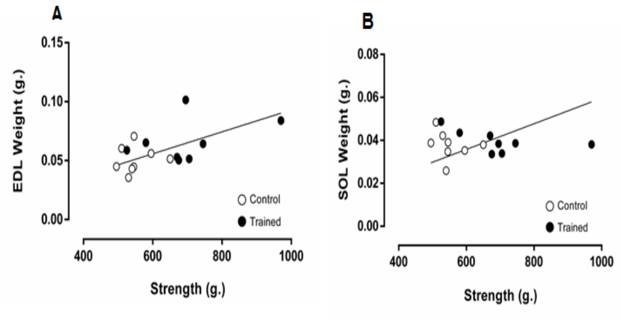

Figure 2. (A) Pearson correlation between animal's strength and EDL weight (r = 0.53, p = 0.03) and (B) Pearson correlation strength and SOL weight (r = -0.18, p = 0.48).

The table 4 and table 5 shows the effect size (control vs. strength training) and their respective magnitudes.

Table 4.
Cohen's *d* effect sizes of the comparison between control and trained groups variables.

	Effect Size	Magnitude
Body Weight (g.)	1.47	Large effect
SOL Relative Weight(g/BW)	-0.38	Small effect
EDL Relative Weight(g/BW)	-1.20	Large effect
AChE Activity in SOL	3,95	Large effect
AChE Activity in EDL	-4,14	Large effect

Table 5.
Cohen's *d* effect sizes of the comparison between control and trained groups strength levels.

	Effect Size	Magnitude
Week 4	-5.32	Large effect
Week 8	-5.14	Large effect

Discussion

Our data demonstrated significant increases in AChE activity in the SOL muscle in accordance with the results of the Gorzi et al. (2013), which have evaluated A12 isoform of AChE after endurance training with running. In that study, the authors suggested that the increased AChE activity related to augment resistance to fatigue was due to the higher storage capacity and consequently greater release of acetylcholine in the neuromuscular junction by motoneurons (Gorzi et al., 2013). According to Navarrete & Vrbova (1983), large magnitude adaptations to the exercise are expected as the isometric contraction of the slow contraction muscles are tonically activated.

Studies of Pregelj & Sketelj (2002) have used the hindlimb suspension model to evaluate the AChE expression in slow and fast rat muscles. This model was adapted from Morey et al. (1979), which have evaluated low gravity effects, an issue very restricted in space research. In the soleus muscles unloaded for 8 days by hindlimb suspension, AChE mRNA levels were not different from those in the control soleus muscles. In contrast, in the suspended animals, AChE transcripts in the EDL muscles decreased to about 80% of control levels (Pregelj & Sketelj, 2002). Those findings indicate that depending on the model of exercise, AchE activity can undergo differentiated adaptations in SOL and EDL muscles. Pregelj & Sketelj (2002) induced an overload by resection of gastrocnemius, whereas in our study, successive loads were added in the rat tail. Thus, we believe that the model used in the present study is a better approximation of the human reality. Our protocol in rats mimicks the isometric strength training used in human strategies of training (Kraemer & Ratamess, 2004; Figard et al., 2006), thereby, it is likely that the AchE activity adaptations in the SOL and EDL muscles could be similarly observed in humans.

We have also hypothesized that AChE synthesis is changed in the SOL and EDL muscles in animals that underwent the isometric strength training, consequently leading to a higher AChE activity. In fact, different stressors can acutely modify the gene expression of this enzyme (Kaufer et al., 1998). This can be underpinned by the fact that the phosphorylation of Elk-1 can induces AChE activation (Xu et al., 2015). It is noteworthy that Elk -1 phosphorylation is one advanced step of MAPK /ERK Ca^{+2}-dependent pathways (Puls et al., 2002).

Studies of Kaufer et al. (1998) have demonstrated that the c-fos protein show a greater expression in DNA promoter region that codify the AChE after swimming forced or administration of inhibitors of AChE. Proteins of the fos family need to be associated to others nuclear proteins to regulate gene expression, and the set of proteins defines whether the gene is repressed or expressed (Kovacs, 1998). Thus, it is necessary to consider the possible involvement of post-translational mechanisms in the regulation of the AChE (Pregelj & Sketelj, 2002).

Indeed, these two proposals can explain the reduction observed in the EDL muscle AChE activity. Not surprisingly, ours results agree to the others authors that observed reduction (Kaufer et al., 1998; Jasmin & Gisiger, 1990; Nikbin et al., 2020) or no significant difference (Farzi et al., 2019) in the activity of AChE using different exercise protocols. Thus, in this preliminary work we have underpinned future studies that might investigate molecular changes related in these responses observed in AChE activity.

In addition, we must consider that the protein expression can be different in several muscle types. Even these differences occur in the SOL and EDL muscles, which can be due to different muscle activation during the exercise (Pregelj & Sketelj, 2002). Our study demonstrated changes with different effect size's magnitude between SOL and EDL relative weight. In fact, in the isometric strength training, the SOL muscle contraction is tonic whereas in the EDL muscle, the contraction is phasic upon the same model of exercise (Navarrete & Vrbova, 1983). This is in accordance with the observation of Gaspersic et al. (1999), which have shown that when EDL is exposed to a pattern of muscle activation, the AChE activity is reduced. The authors justified this change in EDL due the reduction the expression of catalytic subunities of AChE in this condition.

As for zoometric changes, we observed increasing in the SOL and EDL's weight, and these results agree with previous experimental protocol of isotonic strength training (Tamaki et al., 1992). Tamaki et al. (1992) demonstrated the validation of the use of muscle weight/body ratio weight ratio to measure the hypertrophy, or atrophy in comparative experiments with rats. Thus, even using a lower overload than the initial protocol of Lac & Cavalier (1999), we believe that this was effective in producing muscle hypertrophy.

Finally, the strength increases in the training group, this confirm the efficacy of the training protocol. Obviously, these observations agree with previous studies with strength training (Lac & Cavalier, 1999; Tamaki et al., 1992). The isometric strength has been extensively studied. Nevertheless, our study is the first to analyze the progression of strength gains. For this, we used the Bertelle and Mira (1995) protocol to be a non-invasive method. Thereby, we verified a large magnitude in muscle strength in the trained group after 4th and 8th week. New studies involving autonomic (Costa e Silva et al., 2019), hormonal (Pereira et al., 2022; Galaviz Berelleza et al., 2021), other neuromuscular responses (Le-Cerf Paredes et al., 2022) and human applied models (Sosa Izquierdo et al., 2024) are still required to extrapolate our findings.

Conclusion

Therefore, based on AChE activity alterations, our results indicated the expected gain of physiological benefits of IST in comparison to the control group. Additionally, we observed that the adaptations (biochemical, zoometric and functional) could be occurring in a different manner in fast and slow muscles elicited by IST, providing a better adaptation to this type of exercise/stress and likely towards a more efficient metabolic demand of these muscles.

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

Rodrigo Rodrigues da Conceição	rodriguescontato1@hotmail.com	Autor/a
Roberto Laureano-Melo	laureanomelor@gmail.com	Autor/a
Cláudio da Silva Almeida	claudiodasilvaalmeida@gmail.com	Autor/a
Alba Cenélia Matos da Silva	albalina30@gmail.com	Autor/a
Anderson Luiz Bezerra da Silveira	andlbs@yahoo.com.br	Autor/a
Renato Vidal Linhares	renatolinharesjf@gmail.com	Autor/a
Michelle Porto Marassi	portomarassi@gmail.com	Autor/a
Monica Akemi Sato	monica.akemi.sato@gmail.com	Autor/a – Traductor/a
Gisele Giannoco	ggiannocco@gmail.com	Autor/a
Gabriel Costa e Silva	fisiologia.costaesilva@gmail.com	Autor/a
Wellington Côrtes	wscortes64@gmail.com	Autor/a