

Moderate Physical Exercise and Purinergic Signaling: The Impact of Ectonucleotidases on Platelets and Lymphocytes

Andréia Machado Cardoso^{1,2*}, Margarete Dulce Bagatini^{1,2}, Vera Maria Morsch², Aline Mânica² and Maria Rosa Chitolina Schetinger²

¹Federal University of Southern Frontier, Chapecó Campus, Chapecó/SC, Brazil

²Post-Graduation Program in Toxicological Biochemistry, Biochemistry and Molecular Biology Department of Federal University of Santa Maria, Santa Maria, Brazil

Short Communication

The aim of this letter is to summarize the impact of ectonucleotidases activities on platelets and lymphocytes in a model of moderate physical exercise: rats submitted to swimming training.

A vast body of evidence during the last few decades has shown the clear benefits of moderate physical exercise to health. The immune and cardiovascular functions improvements are two of the main positive factors triggered by exercise [1-3]. The beneficial effects from exercise will be achieved chronically, due to body metabolic adaptations related to each acute bout of exercise. However, during the acute exercise practice, that is, during a single bout of exercise, the organism is submitted to a stressful state. These apparently harmful effects of the acute exercise are necessary to the adaptations that will result an enhancement in cardiovascular and immune responses [1,3-5].

One of the mechanisms that are related to inflammatory and platelet responses is the purinergic system. The purinergic system encompasses receptors that respond to extracellular purines, which are designated as P1 and P2 purinoceptors, purines, and (3) a cascade of enzymes that regulate the concentration of purines near the cell surface [6]. Following its release into the extracellular milieu, adenosine triphosphate (ATP) can be rapidly hydrolyzed in a stepwise manner into adenosine diphosphate (ADP) and adenosine monophosphate (AMP) by eNTPDases (ectonucleoside triphosphate diphosphohydrolase) family. AMP produced can be converted into adenosine by ecto-5'nucleotidase (CD73), and adenosine, in turn, can be hydrolyzed into inosine by adenosine deaminase (ADA) [6]. These enzymes are found anchored in the cellular membrane of immune cells and platelets and regulate the action of nucleotides and adenosine in these cells [7]. In lymphocytes, ATP promotes activation followed by pro-inflammatory effects and adenosine is considered a potent anti-inflammatory molecule. On platelets, ATP and ADP are pro-aggregating molecules while adenosine inhibits platelet aggregation [7-9].

Considering that the whole mechanisms by which exercise produces health improvement are not well assigned and the importance of ectonucleotidases and ADA activities on lymphocytes and platelet responses, we hypothesized that the benefits of exercise on immune and cardiovascular functions are intimately linked to purinergic system enzymes regulation. Thus, our studies regarding to the role of ectonucleotidases on platelets and lymphocytes signaling in response to acute and chronic moderate exercise started on 2010. Rats were used as animal models of moderate aerobic swimming training [10]. Table 1 shows our main findings related to the enzyme activities modulation in response to both acute and chronic exercise [10,11].

In lymphocytes our findings demonstrated that chronic exercise has the ability to decrease NTPDase (hydrolyzing ATP and ADP) activity and has no effects on ADA activity. Since ATP is a danger signal and acts activating lymphocytes, we can infer that the reduction of NTPDase activity is occurring due to the less ATP available in the extracellular milieu. The reduction in the ATP concentration is linked to an anti-inflammatory status.

Moderate Exercise	Platelets					Lymphocytes		
	NTPDase (ATP)	NTPDase (ADP)	E-NPP	CD73	ADA	NTPDase (ATP)	NTPDase (ADP)	ADA
Acute	é	é	NC	é	é	ê	ê	ê
Chronic	NC	é	NC	NC	NC	ê	ê	NC

Table 1: The resume of changes in ectonucleotidase activities in response to acute and chronic moderate exercise. é: increase; ê: decrease; NC: no change

Interestingly, acute exercise bout also triggered a decrease on lymphocytic purinergic system enzymes activities. According to Gorman and Feigl [12], during exercise, ATP in plasma is rapidly broken down to ADP, AMP and adenosine by nucleotidases in the plasma and on the surface of red blood cells in order to promote vasodilatation. Thus, what becomes clearly evident is that during exercise, there is a great involvement of purinergic system on tuning the levels of signalling molecules such as ATP, ADP and adenosine and that an augment of purinergic enzymes activities can be expected. However, a reduced NTPDase activity in lymphocytes verified in our study was probably promoted because of the pro-inflammatory responses that are involved during the exercise practice [5]. Even though there is a big amount of ATP being released, the NTPDase present in lymphocytes is not activated. Then, the ATP will be available to bind the P2 receptors and induce lymphocytic activation and amplify the pro-inflammatory responses [5]. The reduction in ADA activity can be explained by both reduced adenosine available and/or reduction in ADA activity in order to promote more available adenosine in the medium, which has anti-inflammatory properties. Taken together, it suggests that the modulation of purinergic signalling can be described as another mechanism that contributes to the anti-inflammatory effects of chronic exercise. In other words, with each exercise session that promotes 'small' proinflammatory responses, the organism become adapted and promotes the subsequent release of anti-inflammatory cytokines and the modulation of immune cells already described by review by Gleeson et al. [5], although this last statement must be further investigated.

On platelets, chronic exercise produced an augment on NTPDase (hydrolyzing ADP). Until now, this is one of our main findings.

***Corresponding author:** Andréia Machado Cardoso, Universidade Federal da Fronteira Sul, Campus Chapecó, Chapecó/SC, Brasil, Av. Fernando Machado, 108 E • Centro CEP 89802-112, Tel: +55 49 2049-1401; E-mail: deiaa.mc@gmail.com

Received September 15, 2015; **Accepted** October 28, 2015; **Published** October 30, 2015

Citation: Cardoso AM, Bagatini MD, Morsch VM, Mânica A, Schetinger MRC (2015) Moderate Physical Exercise and Purinergic Signaling: The Impact of Ectonucleotidases on Platelets and Lymphocytes. Single Cell Biol S1: 005. doi:10.4172/2168-9431.S1-005

Copyright: © 2015 Cardoso AM, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Since NTPDase (ADP) activity is augmented, it means that more ADP is being hydrolyzed [9] and it could explain one of the training mechanisms on thromboregulation. Since less concentration of ADP is in the microenvironment and ADP is the most important molecule that pursues pro-aggregant action, the platelet aggregation occurs in low intensity [9]. This training effect could be understood as one of the main protector actions of chronic exercise on cardiovascular health.

Acute exercise produced an augment on NTPDase (hydrolyzing ATP and ADP), CD73 and ADA activities. Some studies [13,14] have shown that during exercise, red blood cells may control coronary blood flow by releasing ATP in areas of low oxygen tension caused by increased myocardial oxygen extraction. This increase in ATP and its metabolite (ADP, AMP, and adenosine) concentrations in the bloodstream, although being released by erythrocytes, may explain the rise in ectonucleotidase activities as a result of a single bout exercise found in our work, since these enzymes are present on the surface of platelets and probably are in contact with nucleotides released from red cells. A study developed by Yegutkin et al. [15] has assessed changes in platelet ectonucleotidase activities in response to an acute exercise. They showed that strenuous exercise significantly augments platelet activity via transient ADP release, producing acute prothrombotic responses. In contrast, our study indicated an augment in the whole nucleotide hydrolysis, including ADP. These differences on findings probably are related to the intensity of exercises, suggesting that ectonucleotidases, regarding moderate exercise, respond differently from ectonucleotidases regarding strenuous exercise.

In conclusion, our studies have confirmed a great involvement of purinergic system enzymes in the regulation of immune cells and platelets. However, the specific mechanisms have to be deeply investigated and the role of other purinergic components than enzymes should be carefully analyzed. To achieve this need, currently, we are carrying out studies using knockout mice for NTPDases and some purinergic receptors to unveil the specific mechanisms by which purinergic system is altered by physical exercise and the implications of these alterations in immune cells and platelets. We hope to have some interesting news very soon that helps to explain the benefits of exercise on immune and cardiovascular functions.

Acknowledgments

The authors wish to thank Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo à Pesquisa do Rio Grande do Sul

(FAPERGS), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Instituto Nacional de Ciência e Tecnologia (INCT) and Rede Instituto Brasileiro de Neurociência (IBN-Net).

References

1. Pedersen BK (2006) The anti-inflammatory effect of exercise: its role in diabetes and cardiovascular disease control *Essays Biochem* 42: 105-17.
2. Prasad DS, Das BC (2009) Physical inactivity: a cardiovascular risk factor. *Indian J Med Sci* 63: 33-42.
3. Pedersen BK (2011) Exercise-induced myokines and their role in chronic diseases. *Brain Behav Immun* 25: 811-6.
4. Whyte JJ, Laughlin MH (2010) The effects of acute and chronic exercise on the vasculature. *Acta Physiol (Oxf)* 199: 441-50.
5. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, et al. (2011) The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nature Rev Immunol* 11: 607-615.
6. Cardoso AM, Schetinger MR, Correia-de-Sá P, Sévigny J. (2015b) Impact of ectonucleotidases in autonomic nervous functions. *Auton Neurosci* 191: 25-38.
7. Junger WG (2011) Immune cell regulation by autocrine purinergic signaling. *Nature Rev Immunol* 11: 201-212.
8. Bakker WW, Poelstra A, Barradas K, Mikhailidis MA (1994) Platelets and ectonucleotidases. *Platelets* 5: 121-129
9. Atkinson B, Dwyer K, Enjyoji K, Robson SC (2006) Ectonucleotidases of the CD39/NTPDase family modulate platelet activation and thrombus formation: potential as therapeutic targets. *Blood Cells Mol Dis* 36: 217-222
10. Cardoso AM, Abdalla FH, Bagatini MD, Martins CC, Zanini D, et al. (2015a) Swimming training prevents alterations in ecto-NTPDase and adenosine deaminase activities in lymphocytes from N^ω-nitro-L-arginine methyl ester hydrochloride induced hypertension rats. *J Hypertens* 33: 763-72
11. Cardoso AM, Bagatini MD, Martins CC, Abdalla FH, Zanini D, et al. (2012) Exercise training prevents ecto-nucleotidases alterations in platelets of hypertensive rats. *Mol Cell Biochem* 371: 147-56.
12. Gorman MW, Feigl EO (2012) Control of coronary blood flow during exercise. *Exerc Sport Sci Rev* 40: 37-42.
13. Farias M, Gorman MW, Savage MV, Feigl EO (2005) Plasma ATP during exercise: possible role in regulation of coronary blood flow. *Am J Physiol Heart Circ Physiol* 288: 1586-1590
14. Gorman MW, Rooke GA, Savage MV, Jayasekara MPS, Jacobson KA, et al. (2010) Adenine nucleotide control of coronary blood flow during exercise. *Am J Physiol Heart Circ Physiol* 299: 1981-1989.
15. Yegutkin GG, Samburski SS, Mortensen SP, Jalkanen S, Gonzalez-Alonso J (2007) Intravascular ADP and soluble nucleotidases contribute to acute prothrombotic state during vigorous exercise in humans. *J Physiol* 579: 553-564.

This article was originally published in a special issue, [Progress in Single Cell Technology](#) handled by Editor(s). Dr. Yusuf Tutar, Cumhuriyet University, NJ, Turkey