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Letter to the editor

Exercise *vs.* high altitude therapy

Francesco Misiti*

Department of Human Sciences, Society and Health, University of Cassino and Southern Lazio, Cassino 03043, Italy

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Dear Editor,

The metabolic and therapeutic effects of regular exercise on lifestyle-related chronic disease have been long established, but the molecular bases for adaptive changes in metabolic functions remain an area of intense research.

Recently, an elegant study[1] demonstrated that faster acclimatization to high altitude upon re-ascent depends on degradation of equilibrative nucleoside transporter (eENT1), localized on the external face of erythrocytes, induced by a signaling pathway involving adenosine binding to the specific erythrocyte adenosine receptor A2B (ADORA2B). This eENT1 deletion allows for rapid accumulation of plasma adenosine to counteract hypoxic tissue damage. Of note, reduced eENT1 resulting from initial hypoxia is maintained upon re-ascent in humans or re-exposure to hypoxia in mice.

The reported plasma adenosine levels were almost double upon re-ascent to high altitude than on the first hypoxia exposure at the same altitude for 1 day.[1] Intriguingly, sphingosine 1-phosphate (S-1P), a bioactive signaling lipid generated at high levels in erythrocytes, responsible for triggering O_2 delivery under hypoxic conditions, displayed the same trend as elevated extracellular adenosine.[2] Interestingly, the role of adenosine in adaptive mechanisms has also been implicated in the field of exercise training.[3] Exercise affects the purinergic system in erythrocytes and platelets.[4] In particular, increases in adenosine triphosphate (ATP) and its metabolites in blood plasma following exercise have been related to the ability of red blood cells to release ATP in areas of low oxygen tension, as well to rise ectonucleotidase (NTPDase) activities in platelets and red blood cells. It would be interesting to evaluate the levels of eENT1 and S1P in erythrocytes, after targeted exercise interventions based on factors such as mode, intensity, or duration, with a translational perspective to an adaptive mechanism involved in exercise training. It should be noted that these results could be of interest for our understanding of the mechanisms underlying hypoxia related pathologic conditions, such as cardiovascular, hemolytic, and respiratory diseases, and the maintenance of metabolic and functional capacity with aging. More experimental data are needed to confirm the mechanisms reported here. Nonetheless, eENT1 and S1P in erythrocytes may enhance the effects of exercise training without exposure to high altitude. Exercise intervention is an effective and inexpensive alternative to high altitude therapy, easy to access, and not limited to geographic conditions and timing of exposure to high altitudes.

Competing interests

The author declares that he has no competing interests.

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* *E-mail address:* f.misiti@unicas.it

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