Palestrica of the third millennium – Civilization and Sport
Vol. 15, no. 4, October-December 2014, 321–325

Influence of acute exposure to hypobaric hypoxia and ozone, and of lycopene administration on the tissue oxidant/ antioxidant balance in physical exercise studied in the myocardium

Influenţa expunerii acute la hipoxie hipobară, ozon şi administrării de licopin asupra balanţei tisulare oxidanţi/antioxidanţi în efort fizic studiat în miocard

Ágnes Simon-Ugron[1], Simona Tache[2]
[1]Faculty of Physical Education and Sport,"Babeş-Bolyai" University Cluj-Napoca
[2]"Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca

Abstract

Background. The antioxidant effects of lycopene, evidenced in vitro and in vivo under pathological conditions, led us to study in an experimental model of complex combined stress (exposure to moderate hypobaric hypoxia and ozone, and physical exercise) the acute changes in the tissue oxidant/antioxidant (O/AO) balance following lycopene supplementation.

Aims. The influence of acute exposure to hypobaric hypoxia and ozone and of lycopene supplementation on tissue redox homeostasis under physical exercise conditions was studied in the myocardium.

Methods. The research was performed in 6 groups of white male Wistar rats: group I - control group, sedentary rats under normoxia conditions; group II - sedentary rats exposed to combined acute stress: hypobaric hypoxia (corresponding to a 2500 m altitude) and O_3; group III - animals exposed to combined acute stress – moderate hypoxia + O_3 – followed by exercise, under normoxia conditions; group IV - sedentary rats under normoxia conditions, with lycopene administration; group V - animals exposed to combined acute stress – moderate hypoxia + O_3 – followed by lycopene administration; group VI - animals exposed to combined acute stress – moderate hypoxia + O_3 – followed by lycopene administration and daily exercise, under normoxia conditions. Exposure was simulated in the hypobaric chamber for 3 days, 20 hours a day, at 2500 m. Groups III and VI were trained daily for 3 days under normoxia conditions, using the swimming test. Groups IV, V and VI received 0.0375 mg/kg body weight lycopene by oral gavage (before exercise for group VI), daily. In order to measure the indicators of the oxidant/ antioxidant (O/AO) balance, tissue samples were collected from the myocardium. On day 3, the following were determined: malondialdehyde (MDA), protein carbonyls (PC), hydrogen donor capacity (HD) and total sulfhydryl (SH) groups.

Results. Our experimental results obtained in animals that were exercise trained for 3 days and subjected to combined acute stress – hypobaric hypoxia and O3 – and lycopene administration, support the favorable effects of lycopene as an effective antioxidant in the myocardium under exercise conditions.

Conclusions. Lycopene administration in animals subjected to combined acute stress – hypobaric hypoxia and O_3 – followed by exercise determines an increase in oxidative stress (OS) on account of MDA and PC in the myocardium, compared to control animals.

Key words: acute exposure, hypobaric hypoxia, ozone, lycopene, oxidant/antioxidant balance, physical exercise, myocardium.

Rezumat

Premize. Efectele antioxidante ale Licopinului, evidenţiate in vitro şi in vivo în condiţii patologice, ne-au determinat să studiem pe un model experimental de stres complex combinat (expunere la hipoxie hipobară moderată, ozon şi efort fizic), modificările acute ale balanţei oxidanţi/ antioxidanţi (O/AO) la nivel tisular, după suplimentare cu Licopin.

Obiective. S-a studiat influenţa postexpunerii acute la hipoxie hipobară, ozon şi suplimentării cu Licopin asupra homeostaziei redox tisulare postefort la nivelul miocardului.

Metode. Cercetările au fost efectuate pe 6 loturi de şobolani albi masculi rasa Wistar: Lotul I - control, sedentari în condiţii de normoxie; Lotul II - animale sedentare, expuse la stres combinat acut - hipoxie hipobară (corespunzător altitudinii 2500 m) şi O_3; Lotul III - animale expuse la un stres acut combinat - hipoxie moderată şi O_3 - urmat de efort, în condiţii de normoxie; Lotul IV - animale sedentare în condiţii de normoxie, cu administrare de Licopin; Lotul V - animale sedentare expuse la stres

Received: 2014, April 24; *Accepted for publication:* 2014, May 26;
Address for correspondence: Faculty of Physical Education and Sport, "Babeş-Bolyai" University, Cluj-Napoca, Pandurilor Str. No. 7, Romania
E-mail: uagi77@yahoo.com
Corresponding author: Ágnes Simon-Ugron

Copyright © 2010 by "Iuliu Haţieganu" University of Medicine and Pharmacy Publishing

combinat acut - hipoxie hipobară şi O_3 - urmat de administrare de Licopin; Lotul VI– animale expuse la un stres acut combinat - hipoxie moderată şi O_3 - urmat de administrarea de Licopin şi efort zilnic, în condiţii de normoxie. Expunerea simulată s-a făcut la camera hipobarică timp de 3 zile, 20 de ore pe zi la 2500 m. Loturile III şi VI au fost antrenate zilnic timp de 3 zile în condiţii de normoxie, prin proba de înot. La loturile IV, V şi VI s-a administrat zilnic (preefort la lotul VI) Licopin în cantitate de 0,0375 mg/ kg corp, prin gavaj pe cale orală. În vederea determinării indicatorilor balanţei oxidanţi/antioxidanţi (O/ AO) s-au recoltat probe din miocard. În ziua a 3-a s-au determinat: malondialdehida (MDA), proteinele carbonilate (PC), capacitatea donor de hidrogen (DH) şi conţinutul de grupări sulfhidril totale (SH).

Rezultate. Rezultatele noastre obţinute experimental pe animale antrenate la efort fizic timp de 3 zile supuse stresului acut combinat – hipoxie hipobară şi O_3 – şi administrării de Licopin, pledează pentru efectele favorabile ale acestuia ca antioxidant eficient la nivelul miocardului în condiţii de efort.

Concluzii. Administrarea de Licopin la animale supuse unui stres acut combinat – hipoxie hipobară şi O_3, urmat de efort – determină creşterea stresului oxidativ (SO), pe seama MDA şi PC în miocard, faţă de animale martor.

Cuvinte cheie: expunere acută, hipoxia hipobară, ozon, Licopin, balanţa oxidanţi/antioxidanţi, efort fizic, miocard.

Introduction

Hypoxia exposure increases oxidative stress, activates inflammatory cytokines, downregulates ion channels and alters the expression of both pro- and anti-oxidant genes. The results of Singh et al. illustrate the physiological function of nitrite as an eNOS-independent source of NO in the heart, profoundly modulating the oxidative status and cardiac transcriptome during hypoxia (Singh, 2012).

Intermittent hypobaric hypoxia (IHH) and endurance training (ET) are cardioprotective strategies against stress stimuli. Mitochondrial modulation appears to be an important step of the process. Data demonstrates that IHH and ET provide cardiac mitochondria with a more resistant phenotype, although without visible addictive effects, at least under basal conditions. It is suggested that the combination of both strategies, although not additive, results in improved cardiac function (Magelhães, 2013). Moreover, ultrastructural changes in the rat heart tissues depend on the intermittent hypoxia training duration (Rozova, 2012).

Ozone-induced sensitivity to myocardial ischemia-reperfusion injury may be due to promoting levels of oxidative stress as well as inflammatory mediators (Perepu, 2010).

The induced oxidative stress and the alterations in the antioxidant system were normalized by the oral administration of lycopene treatment (Mansour, 2012). A high number of conjugated dienes make lycopene a powerful radical scavenger. Its antioxidant properties are considered to be primarily involved in many beneficial health effects. Pretreatment with tomato extract (1 mg/kg, 2 mg/kg) and vitamin E (50 mg/kg) significantly reduced the malondialdehyde concentration in the heart and significantly lowered the serum AST level in adrenaline treated rats. Myocardial necrosis was significantly prevented by pretreatment. Parvin's results suggest that n-hexane extract of tomato possesses antioxidative properties that may protect the heart against catecholamine induced myocardial infarction (Parvin, 2008). In his studies, Ojha suggested that lycopene possesses significant cardioprotective potential and may serve as an adjunct in the treatment and prophylaxis of myocardial infarction (Ojha, 2013).

Yue observed that the pretreatment of cardiomyocytes with lycopene significantly improved the survival of cardiomyocytes and reduced the extent of apoptosis, and significantly reduced caspase-3 activation. Lycopene may protect against hypoxia/reoxygenation-induced injury by preventing calpain activation (Yue, 2013).

The antioxidant effects of lycopene, evidenced *in vitro* and *in vivo* under pathological conditions, led us to study in an experimental model of complex combined stress (exposure to moderate hypobaric hypoxia and ozone, and physical exercise) the acute changes in the tissue oxidant/antioxidant (O/AO) balance following lycopene supplementation (Ugron et al., 2012a; Ugron et al., 2012b; Simon-Ugron, 2014).

Hypothesis

The influence of acute exposure to hypobaric hypoxia and ozone, and of lycopene supplementation on tissue redox homeostasis under physical exercise conditions was studied in the myocardium.

Material and methods

The research was performed in the experimental laboratory of the Department of Physiology of the "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, on 6 groups of white male Wistar rats (n=10 animals/group), with a weight of 280-300 g, maintained under adequate vivarium conditions. The animal protection legislation in force was respected during the experimental studies.

Groups

The groups were divided as follows:

- group I - control group, sedentary rats under normoxia conditions;
- group II - sedentary rats exposed to combined acute stress: hypobaric hypoxia (corresponding to a 2500 m altitude) and O_3;
- group III - animals exposed to combined acute stress – moderate hypoxia + O_3 – followed by exercise, under normoxia conditions;
- group IV - sedentary rats under normoxia conditions, with lycopene administration;
- group V - animals exposed to combined acute stress – moderate hypoxia + O_3 – followed by lycopene administration;
- group VI - animals exposed to combined acute stress – moderate hypoxia + O_3 – followed by lycopene administration and daily exercise, under normoxia conditions.

Normoxia corresponding to the altitude of 363 m, O_2: 20.94%, air pO_2: 117 mmHg;

Methods

a) *Exposure to moderate hypoxia*

Exposure to moderate hypoxia was for 3 days, 20 hours/day, at values of 2500 m, pO_2 – 117 mmHg, 15%, using hypoxic rooms from the Experimental Laboratory of the Departament of Physiology.

b) *Exposure to ozone*

The rats were exposed to ozone for 3 days, 5 min/day, at values of 0.5 ppm, according to EU norms, using an AIR O_3NE Labor apparatus (SC Triox SRL).

c) *Exercise test*

Groups III and VI were trained daily for 3 days under normoxia conditions using the swimming test. The test was performed in a pool with thermostatic water at 23ºC.

d) *Lycopene administration*

Groups IV, V and VI received 0.0375 mg/kg body weight lycopene by oral gavage (before exercise for group VI), daily. Lycopene is a product of Hungaronatura Hungary, imported by SC. Herbavit Srl.

e) *Exploration of the oxidant-antioxidant balance*

Biochemical determinations were performed in the Laboratory for the Study of Oxidative Stress of the Department of Physiology of the "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca.

In order to determine the indicators of the oxidant/ antioxidant balance, tissue samples were collected from the myocardium of the anesthetized animals. The analyzed time moment was day 3.

The following oxidative stress indicators were measured:

– malondialdehyde (MDA), using the fluorescence dosage method according to Conti (2001); concentration values were expressed in *nmol/mg.*

– protein carbonyls (PC); determination of protein carbonyls according to Reznick (1994); concentration values were expressed in *nmol/mg protein*.

The following antioxidant defense indicators were determined:

– hydrogen donor capacity (HD), dosage method according to Janaszewska (2002); values were expressed as per cent of free radical inhibition *(i%)*;

– sulfhydryl (thiol) group content (SH), determination of SH groups according to Hu (1994); values were expressed in *µmol/mg.*

f) *Statistical analysis* was performed using SPSS 19.0 and Microsoft Excel. The data were introduced in a SPSS v.19 database and analyzed with adequate statistical methods. A univariate statistical analysis was used for the description of the studied groups. Quantitative variables were summarized using means ± standard deviations, 95% confidence intervals for the means. According to the laboratory values, the values for the control group were normal. A bivariate stastistical analysis (Pearson correlation, one-way Anova test and LSD post-hoc test) was used to identify the significant association between the groups and between the indicators of the tissue O/AO balance (MDA, PC, HD and SH), with p set at ≤ 0.05 for analyses.

Results

1. *Comparative statistical analysis of the indicators of the tissue O/AO balance*

The indicators of the tissue O/AO balance were compared between sedentary animals and animals performing physical exercise, under normoxia conditions after hypobaric hypoxia and O_3 exposure, and lycopene administration. The majority of the comparisons were significant (Tables I-IV).

The comparative statistical analysis of the indicators of the tissue O/AO balance between the groups is shown in Tables I-IV, and the comparative statistical analysis of the

Table I

Myocardial MDA (values in nmol/mg)

Group	Mean	Std. deviation	Std. error	95% CI		P values
				Lower limit	Upper limit	
Group I	.05700	.004082	.002041	.05050	.06350	I-II= .009; I-III =.000; I-IV=.000; I-V=.000; I-VI=.000; II-III=.000; II-IV=.000; II-V=.000; II-VI=.000; II-IV=.019; III-V=.039; III-VI=.394; IV-V=.000;IV-VI=.003; V-VI=.194
Group II	.09550	.010344	.005172	.07904	.11196	
Group III	.40375	.007544	.003772	.39175	.41575	
Group IV	.43750	.011733	.005867	.41883	.45617	
Group V	.37450	.037350	.018675	.31507	.43393	
Group VI	.39225	.019085	.009543	.36188	.42262	

Table II

Myocardial PC (values in nmol/mg)

Group	Mean	Std. deviation	Std. error	95% CI		P values
				Lower limit	Upper limit	
Group I	.59650	.052571	.026285	.51285	.68015	I-II= .000; I-III =.000; I-IV=.000; I-V=.000; I-VI=.000; II-III=.000; II-IV=.000; II-V=.000; II-VI=.000; III-IV=.000; III-V=.000; III-VI=.000; IV-V=.000; IV-VI=.073; V-VI=.001
Group II	1.15350	.055073	.027536	1.06587	1.24113	
Group III	2.29675	.054021	.027010	2.21079	2.38271	
Group IV	3.17275	.124385	.062192	2.97483	3.37067	
Group V	3.69925	.211457	.105729	3.36277	4.03573	
Group I	.59650	.052571	.026285	.51285	.68015	

Table III

Myocardial HD (values in i%)

Group	Mean	Std. deviation	Std. error	95% CI		P values
				Lower limit	Upper limit	
Group I	49.47825	1.571569	.785785	46.97753	51.97897	I-II= .429; I-III =.000; I-IV=.000; I-V=.001; I-VI=.259; II-III=.000; II-IV=.000; II-V=.000; II-VI=.724; III-IV=.087; III-V=.278; III-VI=.000; IV-V=.009; IV-VI=.000; V-VI=.000
Group II	50.48475	1.617627	.808814	47.91074	53.05876	
Group III	42.84525	1.532041	.766021	40.40743	45.28307	
Group IV	40.59050	.702760	.351380	39.47225	41.70875	
Group V	44.23875	2.966295	1.483148	39.51871	48.95879	
Group VI	50.93075	1.367058	.683529	48.75545	53.10605	

Table IV
Myocardial SH (values in µmol/mg)

Group	Mean	Std. deviation	Std. error	95% CI		P values
				Lower limit	Upper limit	
Group I	.01875	.002500	.001250	.01477	.02273	I-II= .000; I-III =.020; I-IV=.219;
Group II	.02650	.002380	.001190	.02271	.03029	I-V=.889; I-VI=.137; II-III=.083;
Group III	.02325	.004646	.002323	.01586	.03064	II-IV=.006; II-V=.000; II-VI=.011;
Group IV	.02100	.000816	.000408	.01970	.02230	III-IV=.219; III-V=.015; III-VI=.335;
Group V	.01850	.001291	.000645	.01645	.02055	IV-V=.174; IV-VI=.781; V-VI=.107
Group VI	.02150	.001291	.000645	.01945	.02355	

Table V
Indicators of the myocardial O/AO balance in group I

Group I	Mean	Std. deviation	Std. error	95% CI		P values
				Lower limit	Upper limit	
MDA	.05700	.004082	.002041	.05050	.06350	MDA-PC=.860; MDA-HD=.439;
PC	.59650	.052571	.026285	.51285	.68015	MDA-SH=.804; PC-HD=.149;
HD	49.47825	1.571569	.785785	46.97753	51.97897	PC-SH=.012; HD-SH=.174
SH	.01875	.002500	.001250	.01477	.02273	

Table VI
Indicators of the myocardial O/AO balance in group II

Group II	Mean	Std. deviation	Std. error	95% CI		P values
				Lower limit	Upper limit	
MDA	.09550	.010344	.005172	.07904	.11196	MDA-PC=.156; MDA-HD=.025;
PC	1.15350	.055073	.027536	1.06587	1.24113	MDA-SH=.350; PC-HD=.296;
HD	50.48475	1.617627	.808814	47.91074	53.05876	PC-SH=.199; HD-SH=.467
SH	.02650	.002380	.001190	.02271	.03029	

Table VII
Indicators of the myocardial O/AO balance in group III

Group III	Mean	Std. deviation	Std. error	95% CI		P values
				Lower limit	Upper limit	
MDA	.40375	.007544	.003772	.39175	.41575	MDA-PC=.476; MDA-HD=.150;
PC	2.29675	.054021	.027010	2.21079	2.38271	MDA-SH=.546; PC-HD=.141;
HD	42.84525	1.532041	.766021	40.40743	45.28307	PC-SH=.049; HD-SH=.271
SH	.02325	.004646	.002323	.01586	.03064	

Table VIII
Indicators of the myocardial O/AO balance in group IV

Group IV	Mean	Std. deviation	Std. error	95% CI		P values
				Lower limit	Upper limit	
MDA	.43750	.011733	.005867	.41883	.45617	MDA-PC=.324; MDA-HD=.113;
PC	3.17275	.124385	.062192	2.97483	3.37067	MDA-SH=.200; PC-HD=.082;
HD	40.59050	.702760	.351380	39.47225	41.70875	PC-SH=.675; HD-SH=.502
SH	.02100	.000816	.000408	.01970	.02230	

Table IX
Indicators of the myocardial O/AO balance in group V

Group V	Mean	Std. deviation	Std. error	95% CI		P values
				Lower limit	Upper limit	
MDA	.37450	.037350	.018675	.31507	.43393	MDA-PC=.164; MDA-HD=.909;
PC	3.69925	.211457	.105729	3.36277	4.03573	MDA-SH=.025; PC-HD=.972;
HD	44.23875	2.966295	1.483148	39.51871	48.95879	PC-SH=.306; HD-SH=.850
SH	.01850	.001291	.000645	.01645	.02055	

Table X
Indicators of the myocardial O/AO balance in group VI

Group VI	Mean	Std. deviation	Std. error	95% CI		P values
				Lower limit	Upper limit	
MDA	.39225	.019085	.009543	.36188	.42262	MDA-PC=.143; MDA-HD=.197;
PC	3.34750	.180371	.090185	3.06049	3.63451	MDA-SH=.195; PC-HD=.096;
HD	50.93075	1.367058	.683529	48.75545	53.10605	PC-SH=.543; HD-SH=.705
SH	.02150	.001291	.000645	.01945	.02355	

indicators of the tissue O/AO balance in the same group is shown in Tables V-X.

a) *Comparative statistical analysis of the indicators of the myocardial O/AO balance between the groups*

The comparative statistical analysis of the indicators of the myocardial O/AO balance in the studied groups is shown in Tables I-IV.

b) *Analysis of the correlation between the indicators of the myocardial O/AO balance*

The analysis of the correlation between the indicators of the myocardial O/AO balance in the studied groups and significance are shown in Tables V-X.

The analysis of the correlations between the indicators of the tissue O/AO balance evidences significant correlations in the myocardium: in sedentary animals, between PC and SH, group I (Table V), in animals exposed to hypoxia and O_3, between MDA and HD, group II (Table VI), in animals exposed to hypoxia and O_3 followed by physical exercise,

between PC and SH, group III (Table VII), as well as in animals exposed to hypoxia and O_3 followed by lycopene supplementation, between MDA and SH, group V (Table IX);

2. *A comparative analysis of the indicators of the tissue O/AO balance*

In the myocardium of animals acutely exposed to moderate hypoxia and O_3, with lycopene administration (group V) or lycopene administration followed by exercise (group VI), a significant increase in OS on account of PC and an insignificant increase in AO defense on account of SH were found compared to the groups exposed to the same conditions, without lycopene administration (groups II and III). In animals acutely exposed to moderate hypoxia and O_3, with lycopene administration followed by exercise (group VI), a significant decrease in OS on account of PC and changes in AO defense with a significant increase in HD were found compared to animals acutely exposed to moderate hypoxia and O_3, with lycopene administration (group V).

Discussion

Acute exposure to hypobaric hypoxia and O_3 followed by lycopene administration (group V), compared to acute exposure to hypobaric hypoxia and O_3 (group II), determines a significant decrease of MDA and HD and a significant increase of PC and SH in the myocardium.

The association of acute exposure to hypobaric hypoxia and O_3 with lycopene administration followed by exercise (group VI), compared to acute exposure to hypobaric hypoxia and O_3 followed by exercise (group III), determines a significant increase of PC and HD in the myocardium.

Acute exposure to moderate hypoxia and O_3, with lycopene administration followed by exercise (group VI), compared to acute exposure to hypobaric hypoxia and O_3 followed by lycopene administration (group V), determines a significant decrease of PC and a significant increase of HD in the myocardium.

Our experimental results obtained in animals that were exercise trained for 3 days and subjected to combined acute stress – hypobaric hypoxia and O_3 – and lycopene administration, on which we found no literature studies, support the favorable effects of lycopene as an effective antioxidant in the myocardium under exercise conditions.

The AO effects of lycopene can be associated with hypoxic preconditioning and with the protective effects of O_3.

Conclusions

1. Lycopene administration in sedentary animals subjected to combined acute stress – hypobaric hypoxia and O_3 – determines an increase in OS on account of MDA and PC in the myocardium, compared to control animals.

2. Lycopene administration in sedentary animals subjected to combined acute stress – hypobaric hypoxia and O_3 – determines a decrease in AO defense on account of HD in the myocardium, compared to control animals.

3. Lycopene administration in animals subjected to combined acute stress – hypobaric hypoxia and O_3 – followed by exercise determines an increase in OS on account of MDA and PC in the myocardium, compared to control animals.

Acknowledgements

This paper is based on researches for the first author's doctoral thesis sustained in 2012 at the "Iuliu Haţieganu" University of Medicine and Parmacy, Cluj-Napoca, Romania

I wish to acknowledge the help provided by Professor Dr. Simona Tache, Nicoleta Decea and Remus Moldovan.

References

Conti M., Moran PC, Levillain P et al. Improved fluorimetric determination of malondialdehyde. Clin.Chem. 1991;37:1273-1275.

Hu ML. Measurement of protein thiol groups and glutathione in plasma. Methods in Enzymology.1994; 233:380-384.

Janazsewska A, Bartosz G. Assay of antioxidant capacity: comparison of four methods as applied to human blood plasma. Scand. J. Lab. Invest. 2002;62:231-236.

Magalhães J, Falcão-Pires I, Gonçalves IO et al. Synergistic impact of endurance training and intermittent hypobaric hypoxia on cardiac function and mitochondrial energetic and signaling. Int J Cardiol. 2013;168(6):5363-5371.

Mansour HH, Tawfik SS. Efficacy of lycopene against fluoride toxicity in rats. Pharm Biol. 2012;50(6):707-711.

Ojha S, Goyal S, Sharma C, Arora S, Kumari S, Arya DS. Cardioprotective effect of lycopene against isoproterenol-induced myocardial infarction in rats. Hum Exp Toxicol. 2013;32(5):492-503.

Parvin R, Akhter N. Protective effect of tomato against adrenaline-induced myocardial infarction in rats. Bangladesh Med Res Counc Bull. 2008;34(3):104-108.

Perepu RS, Garcia C, Dostal D, Sethi R. Enhanced death signaling in ozone-exposed ischemic-reperfused hearts. Mol Cell Biochem. 2010;336(1-2):55-64.

Reznick AZ, Packer L. Oxidative damage to proteins: spectrophotometric method for carbonyl assay. Methods in Enzymology. 1994;233: 357 - 363.

Rozova K, Mankovska I. The effect of intermittent hypoxic training on lung and heart tissues of healthy rats**.** Pneumonol Alergol Pol. 2012;80(4):296-300.

Simon-Ugron Á. Influence of acute hypobaric hypoxia, ozone exposure and lycopene administration on the tissue oxidant/ antioxidant balance in physical exercise studied in the brain. Studia Universitatis "Babeş-Bolyai". Educatio Artis Gymnasticae. 2014. LIX. (1): 89-100.

Singh M, Arya A, Kumar R, Bhargava K, Sethy NK. Dietary nitrite attenuates oxidative stress and activates antioxidant genes in rat heart during hypobaric hypoxia**.** Nitric Oxide. 2012;26(1):61-73.

Ugron Á, Tache S, Decea N, Moldovan R. Influenţa expunerii acute la ozon şi hipoxie hipobară asupra balanţei tisulare oxidanţi/ antioxidanţi în efort fizic. Clujul Medical. 2012a;85(3):353-357.

Ugron Á, Tache S, Moldovan R, Decea N. Influence of chronic hypobaric hypoxia exposure and lycopene administration on the tissue oxidant/antioxidant balance in physical exercise. Palestrica of the third millennium Civilization and sport. 2012b;13(2):106-111.

Yue RC, Hu HX, Luo T, Li K, Zhang S, Xu L. Lycopene protects against hypoxia/reoxygenation-injury by preventing calpain activation. Zhonghua Xin Xue Guan Bing Za Zhi. 2013;41(8):654-658.