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INFLUENCE OF ACUTE HYPOBARIC HYPOXIA, OZONE EXPOSURE AND LYCOPENE ADMINISTRATION ON THE TISSUE OXIDANT/ ANTIOXIDANT BALANCE IN PHYSICAL EXERCISE STUDIED IN THE BRAIN

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ABSTRACT. *Background:* The antioxidant effects of lycopene, evidenced *in vitro* and *in vivo* under pathological conditions, made us study in an experimental model of complex combined stress (exposure to moderate hypobaric hypoxia, ozone and physical exercise) the acute changes in the tissue oxidant/antioxidant (O/AO) balance following lycopene supplementation. *Aims***:** The influence of acute hypobaric hypoxia, ozone exposure and lycopene supplementation on tissue redox homeostasis under physical exercise conditions was studied in the brain. *Material and methods:* The researches were performed in 6 groups of white male Wistar rats: group I – control group, sedentary rats under normoxia conditions; group II – sedentary rats exposed to acute combined stress: hypobaric hypoxia (corresponding to a 2500 m altitude) and acute O_3; group III- animals exposed to acute combined stress - moderate hypoxia + acute O_3 -, followed by exercise, under normoxia conditions; group IV - sedentary rats under normoxia conditions, with lycopene administration; group V - animals exposed to acute combined stress - moderate hypoxia + acute O_3 -, followed by lycopene administration; group VI - animals exposed to acute combined stress - moderate hypoxia + acute 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, by the swimming test. Groups IV, V and VI received 0.0375 mg/kg body weight lycopene by oral gavage, (before exercise by group VI), daily. In order to measure the indicators of the oxidant/antioxidant (O/AO) balance, tissue samples were taken from the brain. 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 O_3 – and lycopene administration, support the favorable effects of lycopene as an antioxidant on the brain under rest conditions. *Conclusions:* Lycopene administration in animals subjected to combined acute stress – hypobaric hypoxia and O_3, followed by exercise – determines an increase in AO defense on account of HD in the brain, and a decrease in AO defense on account of SH in the brain, compared to control animals.

Keywords: acute exposure, hypobaric hypoxia, ozone, lycopene, oxidant/ antioxidant balance, physical exercise, brain.

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REZUMAT. ***Influenţa expunerii acute la hipoxie hipobară, ozon şi administrării de licopin asupra balanţei tisulare oxidanţi/ antioxidanţi în efort fizic studiat în creier.*** *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 creierului. *Materiale şi 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 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 creier. 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 la nivelul creierului în condiţii de repaus. *Concluzii:* Administrarea de Licopin la animale supuse unui stres acut combinat – hipoxie hipobară şi O_3, urmat de efort – determină creşterea apărării AO pe seama DH în creier şi scăderea apărării AO pe seama grupărilor SH în creier, faţă de animale martor.

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

Background

Physical activity stimulates various brain chemicals that may leave you feel happier and more relaxed. You may also feel yourself better about your appearance and when you exercise regularly, this can boosts your confidence and improve your self-esteem. Physical exercise has become a potentially

beneficial therapy for reducing neurodegeneration symptoms in Alzheimer's disease (Revilla, S., 2014). Furthermore, physical exercise is a promising nonpharmaceutical intervention to prevent age-related cognitive decline and neurodegenerative diseases. (Bherer, L., 2013)

In his studies, Snigdha suggests mechanisms to improve overall consolidation. Cognitive function remain accessible even with progressing age and it can be re-engaged by both acute and chronic exercise (Snigdha, S., 2014). Moreover, Revilla highlights the fact in his research that different interrelated mechanisms are involved in the beneficial effects of exercise on synaptic plasticity alterations in the 3xTg-AD mouse model (Revilla, S., 2014).

In addition, Hypoxia stimulates cerebral oxidative-nitrative stress (Baylei, D.M., 2009). The prenatal exposure of 1.0 ppm ozone causes embryonic/fetal changes manifested in postnatal levels of noradrenaline concentrations in the brains of rats (Custodio, V., 2010).

On the other hand, lycopene, a carotenoid compound, is a potent antioxidant with demonstrated neuroprotective properties in several experimental models of oxidative damage. Ou's studies suggest that lycopene affords protection against Methylmercury-induced neurotoxicity in cerebellar granule neurons. These beneficial effects of lycopene may be attributable to its roles in preventing mitochondrial dysfunction (Qu, M., 2013). Orally administered lycopene is accumulated in the body, and provided protections against ischemia/ reperfusion-induced brain injury by inducing an increase in SOD activity and inhibiting apoptosis (Fujita, K., 2013).

The antioxidant effects of lycopene, evidenced *in vitro* and *in vivo* under pathological conditions, made us study in an experimental model of complex combined stress (exposure to moderate hypobaric hypoxia, ozone and physical exercise) the acute changes in the tissue oxidant/antioxidant (O/AO) balance following lycopene supplementation (Ugron, Á et al, 2011 and 2012).

Aims

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

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, in 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 researches.

Groups

The groups were divided as follows:

- group I – control group, sedentary rats under normoxia conditions;
- group II – sedentary rats exposed to acute combined stress: hypobaric hypoxia (corresponding to a 2500 m altitude) and acute O_3;
- group III- animals exposed to acute combined stress - moderate hypoxia + acute O_3 -, followed by exercise, under normoxia conditions;
- group IV - sedentary rats under normoxia conditions, with lycopene administration;
- group V - animals exposed to acute combined stress - moderate hypoxia + acute O_3 -, followed by lycopene administration;
- group VI - animals exposed to acute combined stress - moderate hypoxia + acute O_3 -, followed by lycopene administration and daily exercise, under normoxia conditions.
- Normoxia corresponding to the altitude of 363 m, O_2: 20, 94 %, pO_2 air: 117 mmHg;

Methods

a) *The exposure to acute moderate hypoxia*

The 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) *The 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 was trained daily for 3 days under normoxia conditions by 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 by group VI), daily. Lycopene is product to the Hungaronatura Hungary and import to the 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 from the brain, myocardium, lungs and quadriceps muscle of the anesthetized animals were taken. The analyzed time moment was day 3.

The following oxidative stress indicators were measured:

- malondialdehyde (MDA) the fluorescence dosage method, according to Conti (2001); the concentration values are expressed in *nmol/mg.*
- protein carbonyls (PC) determination of protein carbonyls according to Reznick (1994); the concentration values are expressed in *nmol/mg protein*.

The following antioxidant defense indicators were determined:

- hydrogen donor capacity (HD) dosage method according to Janaszewska (2002); the values were expressed as per cent of free radical inhibition *(i%)*;
- sulfhydryl (thiol) group content (SH) determination of SH groups according to Hu (1994); the values are expressed in *μmol/mg.*

f) *Statistical analysis* was performed using SPSS 19.0 and Microsft 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 mean ± standard deviation, 95% confidence interval for means. According to the laboratory values, the values for the control group were normal. A bivariate statistical analysis (Pearson correlation, One-Way Anova 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) was set at $p \leq 0.05$ for analyses.

Results

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 O3 exposure, and lycopene administration. The majority of the comparisons were significant (Tables I-IV).

Comparative statistical analysis of the indicators of the tissue O/AO balance between groups is shown in Table I-IV, and comparative statistical analysis of the indicators of the tissue O/AO balance on the same group is shown in Table V-X.

Comparative statistical analysis of the indicators of the O/AO balance in the brain and between groups

Comparative statistical analysis of the indicators of the O/AO balance in the brain in the studied groups is shown in Table I-IV.

Table I.

MDA in brain (values in nmoli/mg)

Group	Mean	Std. Deviation	Std. Error	I.C. 95%		Values p
				Lower limit	Upper limit	
Group I	.07550	.002646	.001323	.07129	.07971	I-II= **.001**; I-III =**.000**; I-IV=**.000**; I-V=**.001**; I-VI=**.002**; II-III=.503; II-IV=.063; II-V=.866; II-VI=.814; III-IV=.210; III-V=.614; III-VI=.368: IV-V=.087; IV-VI=**.039**; V-VI=.686
Group II	.10350	.001291	.000645	.10145	.10555	
Group III	.10850	.005802	.002901	.09927	.11773	
Group IV	.11800	.015011	.007506	.09411	.14189	
Group V	.10475	.018209	.009105	.07577	.13373	
Group VI	.10175	.006500	.003250	.09141	.11209	

Table II.

PC in brain (values in nmoli/mg)

Group	Mean	Std. Deviation	Std. Error	I.C. 95%		Values p
				Lower limit	Upper limit	
Group I	.69900	.029337	.014669	.65232	.74568	I-II=**.000**; I-III =**.001**; I-IV=**.002**; I-V=**.000**; I-VI=**.000**; II-III=**.000**; II-IV=**.000**; II-V=**.000**; II-VI=**.000**; III-IV=.572; III-V=**.000**; III-VI=**.000**; IV-V=**.000**; IV-VI=**.000**; V-VI=**.000**
Group II	2.23050	.208599	.104300	1.89857	2.56243	
Group III	.32950	.123065	.061533	.13368	.52532	
Group IV	.38125	.146247	.073124	.14854	.61396	
Group V	1.35800	.089499	.044749	1.21559	1.50041	
Group VI	1.84125	.089894	.044947	1.69821	1.98429	

Table III.

HD in brain (values in i%)

Group	Mean	Std. Deviation	Std. Error	I.C. 95%		Values p
				Lower limit	Upper limit	
Group I	35.95525	1.444496	.722248	33.65673	38.25377	I-II=**.001**; I-III=.115; I-IV=**.002**; I-V=**.000**; I-VI=**.000**; II-III=**.033**; II-IV=**.000**; II-V=**.000**; II-VI= **.000**; III-IV=**.000**; III-V=**.000**; III-VI=**.000**; IV-V=**.000**; IV-VI=**.000**; V-VI=.086
Group II	33.32725	.872612	.436306	31.93873	34.71577	
Group III	34.85825	.726419	.363210	33.70235	36.01415	
Group IV	38.32675	.462377	.231189	37.59100	39.06250	
Group V	44.99100	.985500	.492750	43.42285	46.55915	
Group VI	46.19475	.836044	.418022	44.86442	47.52508	

Table IV.

SH in brain (values in μmoli/mg)

Group	Mean	Std. Deviation	Std. Error	I.C. 95%		Values p
				Lower limit	Upper limit	
Group I	.05525	.002500	.001250	.05127	.05923	I-II= **.000**; I-III =**.000**; I-IV=**.000**; I-V=**.000**; I-VI=**.000**; II-III=.210; II-IV=.784; II-V=.112; II-VI=**.000**; III-IV=.132; III-V=.715; III-VI=**.001**; IV-V=.067; IV-VI=**.000**; V-VI=**.002**
Group II	.02750	.001291	.000645	.02545	.02955	
Group III	.03100	.007789	.003894	.01861	.04339	
Group IV	.02675	.000957	.000479	.02523	.02827	
Group V	.03200	.001826	.000913	.02909	.03491	
Group VI	.04175	.003775	.001887	.03574	.04776	

Analysis of the correlation between indicators of the tissue O/AO balance, for each group

Analysis of the correlation between indicators of the O/AO balance, in brain, in the studied groups and significance is shown in Table V-X.

Table V.

The indicators of the O/AO balance at the group I, in the brain

Group I	Mean	Std. Deviation	Std. Error	I.C. 95%		Values p
				Lower limit	Upper limit	
MDA	.07550	.002646	.001323	.07129	.07971	MDA-PC=.944; MDA-HD=.802; MDA-SH=.672; PC-HD=.744; PC-SH=.373; HD-SH=.100
PC	.69900	.029337	.014669	.65232	.74568	
HD	35.95525	1.444496	.722248	33.65673	38.25377	
SH	.05525	.002500	.001250	.05127	.05923	

Table VI.

The indicators of the O/AO balance at the group II, in the brain

Group II	Mean	Std. Deviation	Std. Error	I.C. 95%		Values p
				Lower limit	Upper limit	
MDA	.10350	.001291	.000645	.10145	.10555	MDA-PC=.088; MDA-HD=.584; MDA-SH=.800; PC-HD=.847; PC-SH=.917; HD-SH=**.028**
PC	2.23050	.208599	.104300	1.89857	2.56243	
HD	33.32725	.872612	.436306	31.93873	34.71577	
SH	.02750	.001291	.000645	.02545	.02955	

Table VII.

The indicators of the O/AO balance at the group III, in the brain

Group III	Mean	Std. Deviation	Std. Error	I.C. 95%		Values p
				Lower limit	Upper limit	
MDA	.10850	.005802	.002901	.09927	.11773	MDA-PC=.547; MDA-HD=.069; MDA-SH=.948; PC-HD=.883; PC-SH=.124; HD-SH=.684
PC	.32950	.123065	.061533	.13368	.52532	
HD	34.85825	.726419	.363210	33.70235	36.01415	
SH	.03100	.007789	.003894	.01861	.04339	

Table VIII.

The indicators of the O/AO balance at the group IV, in the brain

Group IV	Mean	Std. Deviation	Std. Error	I.C. 95%		Values p
				Lower limit	Upper limit	
MDA	.11800	.015011	.007506	.09411	.14189	MDA-PC=.207; MDA-HD=.639; MDA-SH=.**049;** PC-HD=.835; PC-SH=.264; HD-SH=.809
PC	.38125	.146247	.073124	.14854	.61396	
HD	38.32675	.462377	.231189	37.59100	39.06250	
SH	.02675	.000957	.000479	.02523	.02827	

Table IX.

The indicators of the O/AO balance at the group V, in the brain

Group V	Mean	Std. Deviation	Std. Error	I.C. 95%		Values p
				Lower limit	Upper limit	
MDA	.10475	.018209	.009105	.07577	.13373	MDA-PC=.197; MDA-HD=.337; MDA-SH=.459; PC-HD=.053; PC-SH=.072; HD-SH=.**026**
PC	1.35800	.089499	.044749	1.21559	1.50041	
HD	44.99100	.985500	.492750	43.42285	46.55915	
SH	.03200	.001826	.000913	.02909	.03491	

Table X.

The indicators of the O/AO balance at the group VI, in the brain

Group VI	Mean	Std. Deviation	Std. Error	I.C. 95%		Values p
				Lower limit	Upper limit	
MDA	.10175	.006500	.003250	.09141	.11209	MDA-PC=.658; MDA-HD=.932; MDA-SH=.677; PC-HD=.225; PC-SH=.837; HD-SH=.503
PC	1.84125	.089894	.044947	1.69821	1.98429	
HD	46.19475	.836044	.418022	44.86442	47.52508	
SH	.04175	.003775	.001887	.03574	.04776	

The analysis of the correlations between the indicators of the tissue O/AO balance evidences significant correlations in the brain: in animals exposed to ozone and hypoxia, between HD and SH, group II (Table VI), in sedentary animals receiving lycopene, between MDA and SH, group IV (Table VIII), as well as in animals acutely exposed to hypoxia and O_3 followed by lycopene supplementation, between HD and SH, group V (Table IX);

A comparative analysis of the indicators of the tissue O/AO balance

Observation: group numbering in the figures is with Arabic numerals. Group I – 1; Group II – 2; Group III – 3; Group IV – 4; Group V – 5; Group VI – 6.

In the brain of animals acutely exposed to moderate hypoxia and O_3, with lycopene administration (group V) or with lycopene administration followed by exercise (group VI), a significant increase in AO defense on account of HD was found compared to the groups exposed to the same conditions, without lycopene administration (groups II and III) (Fig. 3). In animals acutely exposed to moderate hypoxia and O_3, with lycopene administration followed by exercise (group VI), a significant increase in OS on account of PC (Fig. 2) and changes in AO defense with a significant increase in SH (Fig. 4) were found compared to animals acutely exposed to moderate hypoxia and O_3, with lycopene administration (group V).

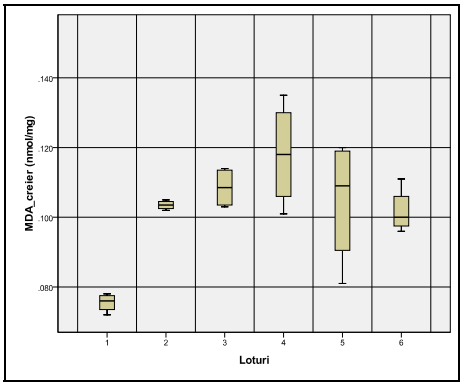

Fig. 1. MDA in the brain

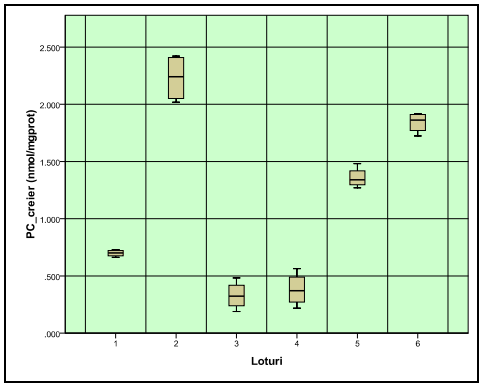

Fig. 2. PC in the brain

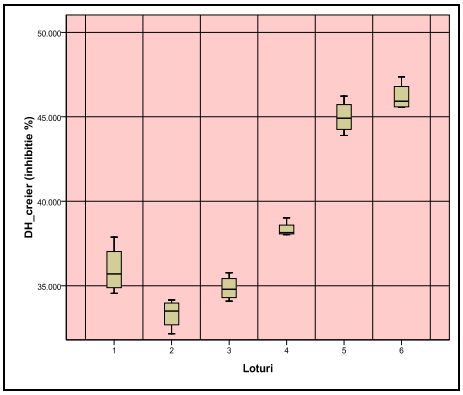

Fig. 3. HD in the brain

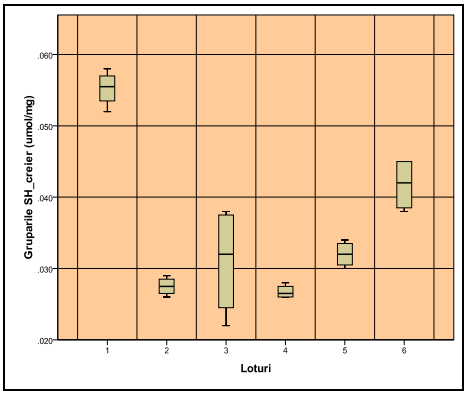

Fig. 4. SH in the brain

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 PC and a significant increase of HD in the brain.

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

Moderate hypoxia and O_3 exposure, with lycopene administration followed by exercise (group VI), compared to acute hypobaric hypoxia and O_3 exposure followed by lycopene administration (group V), determines a significant increase of PC and SH in the brain.

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 antioxidant on the brain under rest 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 brain compared to control animals.
2. Lycopene administration in sedentary animals subjected to combined acute stress – hypobaric hypoxia and O_3 – determines an increase in AO defense on account of HD in the brain, 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 brain, compared to control animals.
4. Lycopene administration in animals subjected to combined acute stress – hypobaric hypoxia and O_3, followed by exercise – determines an increase in AO defense on account of HD in the brain, and a decrease in AO defense on account of SH in the brain, compared to control animals.

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