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Effects of tramadol administration on the oxidant/ antioxidant balance in trained rats

Efectele administrării de tramadol asupra balanței oxidanți/ antioxidanți la șobolani antrenați

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Abstract

Background. Oxidative stress is very intense during high intensity physical exercise, and free radical production represents an important factor of muscle fatigue.

Aims. To assess the effects of tramadol administration on the oxidant/antioxidant balance in trained rats.

Methods. The experimental study was conducted in October-November 2014, at the Physiology Department of the "Iuliu Haţieganu" University of Medicine and Pharmacy in Cluj-Napoca. 24 male Wistar rats were included in the study, over a period of 14 days. They were divided into two homogenous groups: the control group (intraperitoneal physiological serum administration, 1 mg/kg body weight), and the tramadol group (intraperitoneal tramadol administration, 1 mg/kg body weight). The animals were trained daily in the swimming pool, and the oxidant/antioxidant indicators were assessed: malondialdehyde - MDA (free radical marker), hydrogen donors - HD (antioxidant marker), and pain threshold values on the 1st, the 7th and the 14th day of the study.

Results. A significant decrease in MDA values and an increase in HD values were observed among the animals receiving tramadol. Pain threshold values significantly increased in animals receiving tramadol.

Conclusions. Tramadol administration during physical exercise improved the pain threshold and antioxidant defense.

Keywords: tramadol, oxidants/antioxidants, physical exercise.

Rezumat

Premize. Stresul oxidativ este foarte puternic în contextul efortului fizic intens, iar formarea radicalilor liberi reprezintă un factor important și determinant al oboselii musculare.

Obiective. S-au urmărit efectele administrării de tramadol asupra balanței oxidanți/antioxidanți la șobolani antrenați.

Metode. Studiul experimental s-a desfășurat în perioada octombrie-noiembrie 2014 la Disciplina Fiziologie a Universității de Medicină și Farmacie "Iuliu Haţieganu", Cluj-Napoca. 24 șobolani masculi, rasa Wistar au intrat în studiu pentru 14 zile. Au fost împărțiți în 2 loturi omogene: martor (administrare ser fiziologic, 1 mg/kg corp intraperitoneal) și tramadol (administrare tramadol, 1 mg/kg corp intraperitoneal). Animalele au fost antrenate zilnic prin proba de înot, urmărindu-se indicatorii balanței oxidanți/antioxidanți: malondialdehida - MDA (marker al stresului oxidativ), donorii de hidrogen - DH (marker antioxidant), precum și valorile pragului algic în prima, a 7-a și a 14-a zi a studiului.

Rezultate. La animalele lotului care a primit tramadol s-a constatat o scădere semnificativă a valorilor MDA și o creștere semnificativă a valorilor DH. Pragul algic a crescut semnificativ la animalele care au primit tramadol.

Concluzii. Administrarea de tramadol în timpul efortului fizic a determinat creșterea pragului algic și îmbunătățirea apărării antioxidante.

Cuvinte cheie: tramadol, oxidanți/antioxidanți, efort fizic.

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Introduction

Stress is a natural and indispensable phenomenon because it produces adaptive processes. Reactive oxygen species determine cellular lesions translating into the majority of diseases (Radak et al., 2008).

High intensity physical exercise determines high levels of free radicals in skeletal muscles, producing oxidative stress through mechanisms that are not completely understood, including intracellular calcium balance, inflammation, and cellular oxygen consumption.

In time, oxidative stress induces the destruction of lipids, proteins and nucleic acids, leading to a decrease of physical performance, muscle fatigue, muscle injuries and overtraining among athletes (Tache & Staicu, 2010).

At the same time, oxidative stress induces antioxidant defense in order to limit the damaging effects of free radicals. This translates into a decrease of oxidative stress and an increased tolerance of the human body to oxidative stress. Regular aerobic physical exercise and a regular diet have antioxidant effects (Tache et al., 2009).

Physical exercise represents a complex stress: neuromuscular, oxidative, cardiovascular, respiratory, endocrine, metabolic, emotional, as well as a physiological activator of the endogenous opioid system; therefore, pain suppression should be considered an adaptation response (Tache & Staicu, 2010).

Physical exercise improves the quality of life through all its aspects. Exercise-induced analgesia is a relatively new subject of interest in medical research. The implication of the endogenous opioid system, as well as of serotonin and noradrenaline in the modulation of pain, is currently accepted (Koltyn, 2000).

Hypothesis

The aim of this experimental study was to assess the effects of tramadol administration on the pain threshold and oxidative stress balance in trained animals, and to collect data guiding the design of a larger hypothesis-testing study. This was based on previous positive experimental observations regarding the effects of tramadol on aerobic exercise capacity (Ionescu & Tache, 2011).

Material and methods

Tramadol is a centrally acting synthetic analgesic, with low abuse potential, which produces its effects by binding to opioid receptors and by inhibiting noradrenaline and serotonin reuptake (Ionescu et al., 2015). Tramadol is a mix of enantiomers, in which the (+) enantiomer is four times more powerful than the (-) enantiomer, because it binds the μ-opioid receptor (Zacny, 2005). The non-opioid mechanism is powered by the fact that the effects of tramadol are only 50% blocked by naloxone - the main opioid antagonist (Raffa & Friederichs, 2003). It produces its effects by binding plasma proteins, and its analgesic effect has a peak in the first 2-3 hours after administration. It is extensively metabolized in the liver and it is excreted by the kidneys, with a halftime of 6.3 hours (Mohammad et al., 2013; Ozturk et al., 2008; David et al., 2007).

The assessment of lipid peroxides and aldehydes is the most frequent method used to evidence oxidative stress. Malondialdehyde is an oxidative stress indicator used during physical exercise and was assessed from blood samples.

The antioxidant capacity was assessed using the hydrogen donor capacity from animal serum.

Research protocol

a) Period and place of the research

The study was conducted in accordance with ethical standards on animal experimentation, following the approval of the Ethical Committee of "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca. The study and the measurements were carried out between October and November 2014 at the Physiology Department of the same university.

b) Subjects and groups

The research was performed on 24 male Wistar rats, aged 18 weeks, over a period of 14 days. They were divided into two study groups as follows:

Group I: control group: 12 subjects, receiving placebo, i.e. physiological serum, intraperitoneally, 1 mg/kg body weight, once a day, on the 2nd, 5th and 9th day of the study.

Group II: tramadol group: 12 subjects, receiving tramadol, intraperitoneally, 1 mg/kg body weight, once a day, on the 2nd, 5th and 9th day of the study.

c) Tests applied

All the animals performed a training program daily, for a period of 14 days, by swimming in a pool 100/40/60 cm in size, water level 30 cm, water temperature 21-23 degrees Celsius. Supplement weights were placed on the animals' body and they swam as long as they could float without difficulties (Nayanatana et al., 2005).

The following parameters were assessed:

1. The pain threshold was evaluated by the tail flick test on the 1st, 7th and 14th day of the study, using an Ugo-Basile 37215 device, specially designed to test the pain threshold in small laboratory animals. The device exerts a known constant force on the animal's tail situated on a biological Teflon ring. When the pain threshold is reached, the animal withdraws its tail. The time (seconds) until the animal withdraws its tail is registered. The pain threshold was recorded at 4 different moments of each measurement day: at T0, then after 15 minutes (T15), after 30 minutes (T30), and after 60 minutes (T60) from the first evaluation.

2. At the end of the study, blood samples were obtained from the retro-orbital sinus in order to assess MDA and HD, markers of the oxidant/antioxidant balance.

d) Statistical processing

For data processing, we used StatsDirect v.2.7.2. and Microsoft Office Excel 2010, with comparison statistics as described below.

Results

The two investigated groups were compared. There were no statistical differences between the groups regarding age, body mass, and gender.

As shown in Table I, in the placebo group the pain threshold was higher on the 1st day of evaluation, but it was significantly lower on the 7th day, and continued to decrease on the 14th day of the study. In the tramadol group (Table I), the pain threshold was lower on the 1st day of the study, but it began to increase in a significant manner starting with the 7th day of the research, and maintained this

increasing trend until the last day of the study.

When comparing the two groups, the pain threshold was significantly raised by tramadol and physical exercise (i.e. swimming).

The statistical analysis of the oxidant/antioxidant balance indicators yielded the following results: MDA significantly increased in both groups compared to reference values, but when comparing the two groups, MDA was significantly lower in the tramadol group on the 14th day, as shown in Table II. HD significantly decreased in both groups compared to reference values, but this indicator was significantly higher in the tramadol group on the last day of the study, as shown in Table III.

Discussion

The aim of this study was to investigate the effects of the administration of tramadol on the pain threshold and oxidant/antioxidant balance in trained rats.

It was found that tramadol improved all the evaluated parameters. This was also supported by the results of the

Table I

Comparative analysis of pain indicators studied in the two groups and statistical significance.

Day	Group	Time	Mean	SE	Median	SD	Minimum	Maximum	p			
TF, D1	I	T0	5.1	0.050	5.1	0.172	4.90	5.40	T0-T15	0.0023	I-II, T0	0.179
		T15	5	0.041	5	0.141	4.80	5.20	T0-T30	0.123		
		T30	5.2	0.028	5.2	0.095	5	5.30	T0-T60	0.0068		
		T60	5.3	0.041	5.25	0.141	5.1	5.5	T15-T30	0.0038	I-II, T15	0.1916
									T15-T60	0.001		
									T30-T60	0.0234		
	II	T0	5.00	0.052	5	0.181	4.70	5.30	T0-T15	0.1596	I-II, T30	0.896
		T15	5.1	0.062	5.05	0.213	4.80	5.40	T0-T30	0.0152		
		T30	5.2	0.044	5.2	0.154	4.90	5.40	T0-T60	0.1255		
		T60	5.1	0.044	5.1	0.154	4.8	5.3	T15-T30	0.0671	I-II, T60	0.0053
									T15-T60	1		
									T30-T60	0.0671		
TF, D7	I	T0	5.2	0.033	5.2	0.113	5	5.40	T0-T15	0.1834	I-II, T0	9.29×10^{-13}
		T15	5.1	0.057	5.08	0.197	4.80	5.45	T0-T30	0.0892		
		T30	5.3	0.048	5.3	0.165	5.10	5.60	T0-T60	> 0.9999		
		T60	5.2	0.052	5.1	0.180	5	5.55	T15-T30	6.23×10^{-5}	I-II, T15	3.76×10^{-15}
									T15-T60	0.1294		
									T30-T60	0.1094		
	II	T0	6.3	0.054	6.3	0.186	6	6.70	T0-T15	2.17×10^{-5}	I-II, T30	5.43×10^{-16}
		T15	6.6	0.043	6.55	0.148	6.40	6.90	T0-T30	1.92×10^{-6}		
		T30	6.8	0.029	6.8	0.100	6.60	6.95	T0-T60	0.0005		
		T60	7.1	0.074	7	0.256	6.8	7.5	T15-T30	0.0003	I-II, T60	< 0.0001
									T15-T60	0.0005		
									T30-T60	0.0005		
TF, D14	I	T0	5.1	0.025	5.1	0.088	5	5.25	T0-T15	0.0098	I-II, T0	< 0.0001
		T15	4.9	0.058	4.9	0.201	4.60	5.25	T0-T30	0.0122		
		T30	5.3	0.059	5.33	0.206	5	5.60	T0-T60	> 0.9999		
		T60	5.1	0.041	5.1	0.141	4.9	5.3	T15-T30	0.0001	I-II, T15	2.10×10^{-19}
									T15-T60	0.0048		
									T30-T60	0.0035		
	II	T0	7.3	0.078	7.4	0.271	6.85	7.70	T0-T15	5.12×10^{-6}	I-II, T30	3.55×10^{-18}
		T15	7.8	0.068	7.83	0.236	7.45	8.20	T0-T30	1.7×10^{-6}		
		T30	8	0.075	8	0.260	7.60	8.40	T0-T60	3.06×10^{-7}		
		T60	8.3	0.053	8.325	0.185	7.9	8.55	T15-T30	0.0003	I-II, T60	6.87E-23
									T15-T60	2.89×10^{-6}		
									T30-T60	0.0002		
Group I	T0	D1-D7	0.019	T15	D1-D7	0.1926	T30	D1-D7	0.1748	T60	D1-D7	0.2334
		D1-D14	0.8438		D1-D14	0.0015		D1-D14	0.1602		D1-D14	0.002
		D7-D14	0.0322		D7-D14	0.0307		D7-D14	1		D7-D14	0.3804
Group II	T0	D1-D7	5.46×10^{-10}	T15	D1-D7	4.04×10^{-11}	T30	D1-D7	6.16×10^{-12}	T60	D1-D7	0.0005
		D1-D14	1.29×10^{-10}		D1-D14	1.33×10^{-12}		D1-D14	5.34×10^{-14}		D1-D14	1.35×10^{-13}
		D7-D14	7.36×10^{-9}		D7-D14	5.47×10^{-9}		D7-D14	7.74×10^{-9}		D7-D14	0.0005

Table II

Comparative analysis of malondialdehyde studied in the two groups and statistical significance.

Indicator	Group	Moment	Mean	SE	Median	SD	Minimum	Maximum	p		
MDA	I	D1	1.63	0.040	1.64	0.140	1.39	1.80	D1-D14	D1	0.9774
		D14	2.403	0.161	2.695	0.558	1.33	3	0.0024	I-II	
	II	D1	1.63	0.043	1.66	0.148	1.39	1.80	D1-D14	D14	0.0913
		D14	2.04	0.060	2.075	0.208	1.63	2.38	0.0005	I-II	

Table III

Comparative analysis of hydrogen donors studied in the two groups and statistical significance.

Indicator	Group	Moment	Mean	SE	Median	SD	Minimum	Maximum	p		
HD	I	D1	33.12	0.726	33.55	2.514	27.22	36.59	D1-D14	D1	0.7283
		D14	20.96	1.216	20.4	4.211	15.4	29.1	1.44×10^{-6}	I-II	
	II	D1	33.46	0.634	33.99	2.197	28.25	36.69	D1-D14	D14	0.0147
		D14	25.98	1.443	25.75	4.997	16	35.9	0.0006	I-II	

correlation analysis.

The analgesic effect of tramadol is well known and extensively studied. Our results prove that tramadol not only induces analgesia during intense physical exercise, but this effect has nothing to do with its halftime, because we showed that the pain threshold continued to rise 5 days after the last tramadol administration.

Endogenous pain modulation by the opioid system and central serotonin and adrenaline during physical exercise has become a subject of interest since 2006, when Pallazo proved this implication (Pallazo et al., 2006).

Our results demonstrate the antioxidant effects of tramadol when administered during intense physical exercise, i.e. swimming.

In accordance with our findings, an experimental study showed antioxidant effects of tramadol in myocardial ischemia, suggesting its cardioprotective potential (Bilir et al., 2007; Elmawgoud, 2013).

Meanwhile, in our study, tramadol reduced oxidative stress produced by high intensity physical exercise, by decreasing the levels of the MDA marker. This effect could be linked to its important analgesic role, by decreasing muscle pain through opioid receptor and central nervous system modulators.

A clinical study shows positive effects of tramadol administration on aerobic exercise capacity and pain (Ionescu et al., 2015) in subjects suffering from chronic non-specific low back pain. Our results confirm this finding.

On the other hand, in real life, tramadol is prescribed to many subjects suffering from moderate to severe pain, including athletes, because it is not included in the World Anti-Doping Agency Code (1).

As we previously stated, tramadol reduced muscle pain in healthy trained rats during its administration, and its analgesic effect continued 5 days after the last injection. Moreover, it seems that tramadol has benefits on the oxidant/antioxidant balance when administered during intense physical exercise.

Conclusions

1. Tramadol administration during physical exercise improved the pain threshold and antioxidant defense.
2. Taking into account the aforementioned, we strongly recommend that tramadol should be carefully administered to athletes, because it could act as a doping substance.

Conflicts of interests

Nothing to declare.

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