Pharmacological Correction of Testosterone Deficiency during Experimental Myocardial Ischemia

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Experiments on rats with myocardial ischemia modeled by occlusion of the left coronary artery aggravated by alimentary dislipoproteinemia showed that therapy with taurepar (50 mg/kg), a taurine derivative, decreased blood corticosterone concentration and increased the level of endogenous testosterone, which attests to normalization of the compensatory-adaptive and gonadotropic functions of the organism.

Key Words: *myocardial ischemia; testosterone; dislipoproteinemia*; *taurine*

Androgen deficiency and atherogenic dislipoproteinemia (DLP) aggravate the course and prognosis of CHD [5,9,13]. Low free serum testosterone is an independent risk factor of atherosclerosis [10,11]. Apart from increased level of triglycerides (TG) and low-density lipoproteins (LDL), patients with atherosclerosis of coronary arteries are characterized by a diminished level of free testosterone [8,13]. Some studies demonstrated a beneficial effect of testosterone on the therapy of cardiovascular diseases related to improvement of circulation and metabolism in myocardium [15]. It is hypothesized that testosterone improves cardiomyocyte trophicity during myocardial hypertrophy acting via a specific androgen receptors [14]. However, in some cases the therapy with androgen hormones is associated with various side effects such as water and salt retention, enhanced sexual arousal, or anabolic effects [4]. Therefore, the search for the cardiotropic agents capable to eliminating androgen deficiency due to up-regulation of endogenous testosterone is extremely important.

Wide spectrum of pharmacological activities of taurine derivative taurepar synthesized at Department of Neuropharmacology, Institute of Experimental Medicine (North-Western Division of Russian Academy of Medical Sciences) is a basis to consider the drug as an efficient tool for correction of metabolic imbalance accompanying myocardial infarction [2]. The antiischemic action of taurepar results from moderation of lipid peroxidation and restoring activity of enzymes responsible for energy metabolism and antioxidant protection [7].

Our aim was to examine the possibility to using taurepar for correction of testosterone deficiency developing in myocardial ischemia complicated by dislipoproteinemia (DLP).

MATERIALS AND METHODS

Experiments were carried out on random-bred male albino rats (n=100) weighing 230-250 g. The animals were randomized into 5 groups. Group 1 included intact controls and groups 2-5 consisted of rats with DLP produced by feeding a high fat diet including 7.5% food cholesterol, 45% fat mixture (porcine fat and sunflower oil, 2:1 ratio), 500,000 U vitamin D (ergocalciferol) in addition to standard ration for 21 days [12]. On day 22, the left coronary artery in rats of groups 3, 4, and 5 was ligated immediately below the auricula under ether narcosis according to the method of Selye for modeling myocardial ischemia. Starting

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from the postocclusion day 1, group 4 rats were daily treated with taurepar (50 mg/kg *per os* for 7 days) and group 5 rats were treated with a reference drug taurine (500 mg/kg).

Serum levels of testosterone and corticosterone were determined by ELISA using kits for human hormone assay *in vitro* (Khema-Medika) according to manufacturer's protocol. These tests were preceded by titration of all kits, the choice of optimal dilution of the rat blood sera, testing for doubling, and internal standard test. The assays were counted automatically with an Uniplan multichannel spot-color spectrophotometer at λ=450 nm. Total cholesterol (CH), TG, CH of antiatherogenic high density lipoproteins (HDL) were assayed in blood serum by the routine methods with the corresponding kits. The atherogenic index was calculated according to [3].

The data were analyzed statistically with SPSS 11.5 software [1]. The mean values were compared using of one-way ANOVA test at $p<0.05$.

RESULTS

In group 2 rats maintained on a high fat diet, total testosterone decreased by 44.2%, while corticosterone increased by 64% in comparison with the intact rats ($p<0.05$) indicating inhibition of gonadotropic function and activation of the pituitary-adrenal axis (Table 1). Changes in lipid profile of the blood in DIP-simulated rats reliably reflect the state of experimental atherogenic DLP. The levels of total CH and TG increased by 2.5 and 2.6 times, respectively. Simultaneously, HDL CH decreased by 1.6 times, while atherogenic index increased 7-fold.

In group 3 rats (untreated controls) examined in 7 days after occlusion of the left coronary artery, serum concentration of total testosterone decreased by 53.5%, while serum corticosterone increased by 82.7% compared to intact animals ($p<0.05$). Lipid blood indices attested to pronounced damaging effect produced by occlusion of the left coronary artery. While the levels of CH and TG were high, the content of CH in the antiatherogenic HDL decreased 2.8-fold, the atherogenic index increased by 9.6 times in comparison with the corresponding indices of intact rats.

In the group 4 rats (myocardial ischemia treated with taurepar) examined on postocclusion day 7, the ischemia-provoked metabolic shifts in hormonal and lipid profiles were expressed to a lesser degree. The corticosterone level decreased to values observed in intact rats attesting to normalization of the compensatory-adaptive mechanisms, while testosterone level increased by 80% in comparison to the untreated group 3 rats. At the same time, the serum levels of CH and TG decreased by 1.7 and 1.4 times, respectively, in comparison with the control rats. It should be stressed that the content of HDL CH did not differ from values characteristic of intact rats. The potency of taurepar to increase the concentration of HDL CH results in an extra contribution to its anti-ischemic action. The atherogenic index dropped 3.9-fold compared to the control. Thus, changes in the blood lipid profile observed during treatment in rats with occlusion of the left coronary artery aggravated by DLP reaffirms hypolipidemic property of taurepar previously established on the models of induced DLP [6].

Different results were obtained in the group 5 rats treated with the reference drug taurine. In this group,

TABLE 1. Effects of Taurepar and Taurine on Hormonal and Lipid Profiles in Rats during Myocardial Ischemia Aggravated by DLP (*M±SEM*)

Index	Intact rats	Rats maintained on a high fat diet			
		without occlusion	postocclusion day 7 (control)	postocclusion day 7+taurepar	postocclusion day 7+taurine
	group 1	group 2	group 3	group 4	group 5
Testosterone, nmol/liter	4.3±0.2	2.40±0.27*	2.00±0.23*	3.60±0.25*+xo	3.00±0.25*+x
Corticosterone, nmol/liter	17.4±1.7	28.6±2.5*	31.8±3.5*	18.7±1.8+xo	30.0±2.2*
Total CH, mmol/liter	1.28±0.05	3.21±0.17*	3.42±0.11*	2.01±0.10*+	2.84±0.34*
TG, mmol/liter	0.56±0.03	1.46±0.09*	1.42±0.06*	0.99±0.05	1.10±0.06
CH in HDL, mmol/liter	0.60±0.03	0.36±0.04*	0.21±0.02*+	0.54±0.02+xo	0.46±0.02*+x
Atherogenic index	1.1	7.8	10.6	2.7	5.15

Note. $p<0.05$ compared to *intact rats, +group 2 rats, xgroup 3 rats, and ogroup 5 rats.

the serum concentration of corticosterone remained at the same high level as in the untreated rats. On treatment day 7, the testosterone level increased by 50% in comparison with control rats although it remained lower by 30% than that in rats treated with taurepar ($p<0.05$).

By the efficacy of hypolipidemic action, taurine was also somewhat weaker than taurepar. It decreased CH and TG 1.2- and 1.3-fold, respectively. In addition, taurine elevated HDL CH by 2.2 times (although it did not reach the initial level) and only 2-fold decreased the atherogenic index.

Thus, this study showed that in addition to elimination of metabolic disbalance and elevation of HDL CH, the anti-ischemic effect of taurepar includes normalization of gonadotropic function and compensatory-adaptive mechanisms. It can be reasonably hypothesized that due to its cardiotropic and hypolipidemic effects accompanied by involvement in elimination of endogenous testosterone deficiency, taurepar will be useful in the complex therapy of CHD aggravated by DLP and hypogonadism.

REFERENCES

1. A. Bryul' and P. Tsefel', SPSS Software Package: *The Frontier Approach to Analysis, Processing, and Presentation of Statistical Data in Marketing, Sociology, and Medicine*, Ed. V. E. Molot [in Russian], Moscow, St. Petersburg, Kiev (2002).
2. I. S. Zafodskaia, L. K. Khnychenko, and N. S. Sapronov, *Vestn. Ross. Akad. Med. Nauk*, No. 12, 41-44 (2002).
3. A. N. Klimov and N. G. Nikul'cheva, *Lipid and Lipoprotein Metabolism and Its Disturbances* [in Russian], St. Petersburg (1999).
4. M. D. Mashkovskii, *Therapeutic Preparations* [in Russian], Vol. 2, Moscow (1998), pp. 60-61.
5. L. Yu. Morugov, *Klin. Med.*, No. 9, 17-21 (2007).
6. I. V. Okunevich, L. K. Gavrovskaya, and N. S. Sapronov, *Eksp. Klin. Farmakol.*, **70**, No. 2, 48-50 (2007).
7. L. K. Khnychenko, V. V. Bul'on, and N. S. Sapronov, *Ibid.*, **64**, No. 2, 38-40 (2001).
8. W. Barud, R. Palusinski, A. Piotrowska-Swirszcz, *et al., Pol. Merkur. Lekarski.*, **18**, No. 105, 295-297 (2005).
9. E. Debing, E. Peeters, W. Duquet, *et al., Int. Angiol.*, **27**, No. 2, 135-141 (2008).
10. M. Muller, A. W. Van den Beld, M. L. Bots, *et al., Circulation*, **109**, No. 17, 2074-2079 (2004).
11. G. B. Phillips, *J. Clin. Endocrinol. Metab.*, **90**, No. 5, 2708-2711 (2005).
12. N. S. Sapronov, L. K. Khnychenko, I. V. Okunevich, and L. K. Gavrovskaya, *Adv. Exp. Med. Biol.*, **583**, 515-521 (2006).
13. L. Sieminska, C. Wojciechowska, E. Swietochowska, *et al., Med. Sci. Monit.*, **9**, No. 5, CR162-CR166 (2003).
14. L. Smeets and J. J. Legros, *Ann. Endocrinol. (Paris)*, **65**, No. 2, 163-170 (2004).
15. A. Vermeulen, *J. Clin. Endocrinol. Metab.*, **73**, No. 2, 221-224 (1991).