Effect of the Tranquilizer Mebicar on Lipid Metabolism and Lipid Peroxidation on the Model of Hypokinesia in Rats

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Daily 18-hour hypokinesia induces atherogenic shifts in the blood lipid spectrum and activates lipid peroxidation in rats. Mebicar is shown to have a correcting effect on lipid metabolism and on the intensity of lipid peroxidation.

Key Words: *hypokinesia; lipid metabolism; lipid peroxidation*

Stress is known to play a crucial role in the pathogenesis of atherosclerosis [3,8,9], and therefore it makes sense to seek new antiatherosclerotic and hypolipidemic drugs among the tranquilizers [3,10, 11]. Our attention was drawn to the Russian-manufactured mild tranquilizer mebicar, a member of the bicyclic bisurea family, whose effect on lipid metabolism has been demonstrated in clinical studies [5]. In the present study we evaluated the effect of mebicar on the blood lipid spectrum and intensity of lipid peroxidation (LPO) in rats under conditions of hypokinesia. This model was chosen as a high-risk state for atherosclerosis development [1,2,6].

MATERIALS AND METHODS

The experiment was carried out on 75 nonpedigree male albino rats with an initial weight of 180-200 g. The animals were fed standard vivarium chow. For hypokinesia modeling the animals were placed in special closely fitting Plexiglas boxes with free access to food and water for 18 hours each day. During the remaining 6 hours the animals were free and the boxes were cleaned.

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In the first experimental series, performed so as to develop the method, the animals (n=30) were divided into 2 groups: 15 intact rats (group 1) and 15 in a state of hypokinesia (group 2). In series II the rats (n=45) were divided into 3 groups of 15: intact controls (group 1) and animals in a state of hypokinesia receiving intragastrally either twice-distilled water or mebicar (250 mg/kg) (groups 2 and 3, respectively).

On days 7 and 14 of the experiment the animals were weighed, and blood was collected. The total cholesterol (TCH), high density lipoprotein cholesterol (HDL-CH), and triglycerides were measured with diagnostic kits using a Labsystems autoanalyzer. The concentration of phospholipids was determined by the content of lipid phosphorus in a lipid-protein precipitate [7]. LPO intensity was assessed by the blood content of the end LPO product, malonic dialdehyde (MDA), measured in the reaction with 2-thiobarbituric acid [4]. On day 14 the animals were sacrificed and the relative weight of the adrenals was determined.

The exparimental data were processed statistically using the Student t test.

RESULTS

In series I the animals in a state of hypokinesia lost 6.3% (p<0.005) and 14.6% (p<0.001) of their body

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TABLE 1. Blood Content of the Main Lipid Fractions and MDA in Rats of Series I (*M±m*)

Group	Parameter				
	TCH, mmol/liter	HDL-CH, mmol/liter	triglycerides, mmol/liter	phospholipids, mmol/liter	MDA, nmol/liter
Intact	0.98±0.02	0.69±0.08	0.84±0.08	1.59±0.08	1.89±0.11
Hypokinesia, 7 days	1.29±0.10*	0.64±0.01	0.87±0.07	1.05±0.12**	2.19±0.09*
Hypokinesia, 14 days	1.32±0.12**	0.51±0.06**	1.14±0.12**	0.96±0.09**	2.27±0.07**

Note. Here and in Table 2: *$p<0.05$, **$p<0.01$, ***$p<0.001$ differences between the intact and control groups.

TABLE 2. Blood Content of the Main Lipid Fractions and MDA in Rats of Series II (*M±m*)

Group		Parameter				
		TCH, mmol/liter	HDL-CH, mmol/liter	triglycerides, mmol/liter	phospholipids, mmol/liter	MDA, nmol/liter
Intact,	7 days	0.99±0.04	0.77±0.06	0.85±0.09	1.19±0.06	1.87±0.01
	14 days	0.95±0.09	0.74±0.03	0.82±0.12	1.21±0.06	1.82±0.03
Control,	7 days	1.27±0.10**	0.73±0.08	0.98±0.05*	0.99±0.08*	2.03±0.12*
	14 days	1.35±0.06**	0.60±0.05**	1.39±0.19**	0.82±0.15**	2.33±0.19**
Experimental,	7 days	1.14±0.02	0.75±0.08	0.58±0.15++	1.16±0.07	1.93±0.10
	14 days	0.98±0.12++	0.89±0.03+++	0.88±0.05++	1.57±0.05+++	1.81±0.10

Note. +$p<0.05$, ++$p<0.01$, +++$p<0.001$ differences between the control and experimental groups.

weight by days 7 and 14, respectively, in comparison with intact controls. After 14 days of hypokinesia we observed a 35.6% increase of the relative weight of the adrenals in comparison with group 1 ($p<0.001$).

In the lipid spectrum in rats of group 2 on day 7 we observed a 31.6% rise of TCH ($p<0.05$), which attained 34.6% on day 14 ($p<0.01$), whereas HDL-CH on day 14 had dropped by 26% in comparison with group 1 (Table 1). The level of triglycerides was practically unchanged on day 7, but had risen 36% on day 14 in comparison with the intact controls ($p<0.01$). The concentration of phospholipids in animals in a state of hypokinesia dropped by 34 and 40% ($p<0.01$) on days 7 and 14, respectively.

The level of MDA in group 2 rose by 16% ($p<0.05$) and 20% ($p<0.01$) on days 7 and 14 in comparison with group 1. Studying these parameters at the same times in series II, we observed a 5.6% loss of body weight ($p<0.005$) on day 7, which attained 13.2% ($p<0.001$) on day 14, the body weight of the intact and mebicar-treated rats being unchanged.

In group 2 the relative weight of the adrenals increased by 32.1% ($p<0.001$) in comparison with the control group. In group 3 this parameter remained unchanged.

Thus, under conditions of modeled hypokinesia in rats of both experimental series we observed a loss of body weight and hypertrophy of the adrenals by the end of the first week and especially by the end of the experiment. This dynamics may be interpreted as exhaustion of the mechanisms of adaptation to a permanent stress factor. Mebicar prevents the loss of body weight and adrenal hypertrophy, which confirms the stress-protective action of the drug.

A study of the indexes of lipid metabolism in rat blood (Table 2) revealed a 27.8% ($p<0.05$) drop of TCH and a 48.8% ($p<0.001$) rise of HDL-CH in mebicar-treated rats on day 14 in comparison with the control group. The level of triglycerides in the mebicar-treated animals dropped by 41 and 36% on days 7 and 14, respectively, in comparison with the control ($p<0.01$).

The concentration of phospholipids rose by 17% ($p<0.05$) and 91.5% ($p<0.001$) on days 7 and 14, respectively, in comparison with controls.

These shifts in the blood lipid spectrum in group 2 of both series are evidently proatherogenic and confirm the data of other authorities on the disturbances of lipid metabolism in hypokinesia. The hypolipidemic effect of mebicar consists in its ability to prevent these shifts.

Activation of LPO is an important pathogenetic factor of atherogenesis. In the control group under conditions of modeled hypokinesia we observed a 28% ($p<0.01$) rise of MDA, the end product of LPO. In comparison with the control group, in the mebic-

ar-treated group MDA was decreased by 22.3% ($p< 0.01$), which attests to probable antioxidant properties of the drug.

Thus, in our experiments mebicar exhibited a beneficial combination of adaptogenic, hypolipidemic, and, probably, antioxidant effects.

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Antidepressive Effect of O-β-Chloroethyl-para-N-Dimethylphosphinylacetic Acid (Amphazide)

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The antidepressive effects of O-β-chloroethyl-para-N-dimethylphosphinylacetic acid (amphazide) are demonstrated on CBWA tetrahybrid male mice using the "behavioral despair" and "conditioned helplessness" models. The pharmacological effect of a course of amphazide appears more rapidly than that of the tricyclic antidepressant melipramine. The serotonin-positive activity of amphazide manifests itself, in particular, in a heightened reaction of stressed mice to injection of 5-hydroxytryptophan.

Key Words: *organophosphorus compounds; antidepressant; serotonin-positive action*

The creation of new, highly effective antidepressants without marked side effects calls for exploiting original chemical classes. Of particular interest in this connection are the organophosphorus compounds without intrinsic anticholinesterase activity, among which neurotropic drugs [2], including antidepressants [1], are found.

The present study evaluates the antidepressant properties of O-β-chloroethyl-para-N-dimethylphosphinylacetate hydrazide (amphazide).

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MATERIALS AND METHODS

The experiments were carried out on inbred male mice, CBWA tetrahybrids, weighing 19-22 g. Antidepressant activity was assessed using the "behavioral despair" [5,9] and "conditioned helplessness" [8] models.

In the "behavioral despair" model, amphazide (90 mg/kg) was injected intraperitoneally 40 min before testing and then once a day during 10 days, and 24 hours after the last injection the animals were tested again.

In the model of "conditioned helplessness" the total time of escape delay and the total number of

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