A New Activity of N-Cholinolytic Drug Benzohexonium

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We have found that N-cholinolytic drug benzohexonium produces a hypolipidemic effect: it reduces dyslipoproteinemia, fatty infiltration of the liver, and risk of atherosclerotic lesions.

Key Words: *cholinergic systems; ganglionic blockers; benzohexonium; dyslipoproteinemia*

Cholinergic system of the body and acetylcholine are involved in the regulation of vital activities and metabolism intensity including lipid metabolism [9,10]. Previous studies showed that the lipolytic system is sensitive to cholinergic stimulation [11-13]. Impaired lipid and lipoprotein metabolism is closely associated with progression of arterial hypertension (AH), coronary heart disease (CHD), and their complications [3]. Increased tone of the sympathetic system precedes the development of AH and due to hemodynamic and metabolic disorders aggravates this pathology and exacerbates dyslipoproteinemia contributing to structural changes of the arterial wall and heart. Therefore, normalization of high blood pressure and management of dyslipoproteinemia is important for preventing progression of cardiovascular disease. In this regard, medications for managing hypertension with simultaneous correction of blood lipid levels are of practical interest.

Sympathetic system hyperactivity can be corrected with drugs directly blocking central and peripheral adrenergic receptors and possessing adrenolytic activity due to inhibition of catecholamine synthesis and secretion [1,4]. Peripheral nicotinic receptor antagonist benzohexonium also belongs to the class of drugs reducing the tone of the sympathetic nervous system via inhibition of nerve impulse transmission. It is used in clinical practice for treating AH (especially in young patients), bronchoconstriction, peripheral vascular spasm, and to arrest hypertensive crises [4,8].

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Here we studied the effects of benzohexonium on changes in lipid metabolism indicators during experimental dyslipoproteinemia.

MATERIALS AND METHODS

Experiments were carried out on outbred albino male rats (n=100) weighing 230-250 g and guinea pigs (n=60) weighing 300-350 g. For modeling dyslipoproteinemia, the animals were kept on a special hypercholesterol diet (HD) enriched in cholesterol (CH) and fats for 21 day [5,7]. Different animal species were used because of their particular characteristics of lipid profiles. In guinea pigs, CH is primarily concentrated in atherogenic LDL and VLDL, while in rats CH is located primarily in antiatherogenic HDL [3,14].

Experimental animals receiving HD simultaneously received benzohexonium through a tube in a dose of 20 mg/kg. The dose was chosen in our preliminary experiments as optimally effective and not producing side effects. Gemfibrozil (50 mg/kg) was used as the reference drug. The rats and guinea pigs were sacrificed on day 22 after the end of dyslipoproteinemia modeling and appropriate treatment. The animals were deprived of food 18 h before decapitation.

Serum levels of total CH (TCH), CH in antiatherogenic HDL, and triglycerides were determined using kits of reagents on the basis of standardized methods according to manufacturer's instructions (Vital Diagnostics). Atherogenic index (AI) was calculated by Klimov's formula [3].

Lipids in the liver (TCH, triglycerides) and aorta (TCH) were extracted with isopropanol/chlo-

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roform mixture. Lipid content was determined in extracts [5].

Statistical analysis of the results was performed using SPSS 11.5 statistical software [2]. Mean values were compared using one-way ANOVA at $p<0.05$.

RESULTS

Rats kept on HD (group 2) showed increased levels of TCH and triglycerides in the serum (by 2.2 and 2.8 times, respectively) and liver (by 2.5 and 4.8 times, respectively) and elevated TCH in the aorta (by 1.9 times; Table 1). At the same time, the concentration of CH in antiatherogenic HDL was reduced 2-fold in comparison with intact animals (group 1). Atherogenic index increased by more than 6 times. Changes in lipid profile recorded during dyslipoproteinemia modeling completely reflected the status of experimental atherogenic dyslipoproteinemia. A different pattern was observed in the group of rats treated with benzohexonium against the background of HD (group 3): serum TCH decreased by 1.6 times, triglycerides by 3 times, and HDL CH increased by 2 times. In addition, TCH and triglycerides in the liver decreased by 2.4 and 2.2 times, respectively, and TCH in the aorta decreased by 1.8 times. Cholesterol atherogenic index decreased 4-fold in comparison with that in rats receiving HD alone. Reduced lipid infiltration of the aorta and dynamics of cholesterol atherogenic index suggest that benzohexonium has a protective effect on the vascular wall.

In guinea pigs, chronic alimentary dyslipoproteinemia was also characterized by increased levels of lipids in the blood, liver, and aorta (group 2). Serum levels of TCH and triglycerides were elevated by 4.7 and 6 times, respectively, CH in HDL decreased 4-fold. Lipidosis was found in the liver and aorta. Cholesterol atherogenic index exceeded that calculated for intact animals by more than 20 times.

During the treatment of guinea pigs with benzohexonium (group 3), serum level of TCH significantly decreased by 2 times, triglycerides by 1.7 times, and HDL CH (reduced during dyslipoproteinemia) increased by 1.7 times, which attests to lipid-lowering effect of the test ganglionic blocker. Cholesterol atherogenic index decreased by 6 times as a result of reduced TCH and increased CH HDL. The content of TCH in the aorta decreased by 2.3 times, which suggests potential antiatherosclerotic properties of the test drug. In the liver, less severe lipidosis was found: the levels of TCH and triglycerids decreased by 1.5 and 2.0 times, respectively, in comparison with the group of hyperlipidemic guinea pigs (group 2).

Thus, experiments on rats and guinea pigs with modeled dyslipoproteinemia demonstrated that oral administration of nicotinic cholinergic receptor antag-

TABLE 1. Effects of Benzohexonium on Values of Lipid Indicators in Serum, Liver, Aorta and Cholestrol Atherogenic Index in Rats and Guinea Pigs under Nutritional Dyslipoproteinemia, Induced by 21-Day Long HD

Group	Species	Blood lipids, mmol/liter			Tissue lipids, mg/g of wet tissue			
		TCH	TG	CH in HDL	liver		aorta	
					TCH	TG	TCH	AI
1 (intacts)	Rats	1.55±0.07	0.67±0.03	0.60±0.06	2.3±0.1	3.5±0.2	1.9±0.1	1.6
	Guinea pigs	1.01±0.10	0.54±0.07	0.31±0.05	3.4±0.3	4.2±0.6	2.3±0.4	2.2
2 (HD)	Rats	3.51±0.05*	1.90±0.05*	0.30±0.01*	5.9±0.1*	17.0±0.5*	3.7±0.5*	10.7
	Guinea pigs	4.81±0.40*	3.21±0.10*	0.08±0.03*	20.9±1.1*	22.80±0.65*	22.1±0.3*	59.1
3 (benzohexonium+HD)	Rats	2.14±0.20$^+$	0.60±0.01$^+$	0.61±0.06$^+$	2.4±0.1$^+$	7.6±0.4$^+$	2.0±0.2$^+$	2.5
	Guinea pigs	2.2±0.2$^+$	1.84±0.10$^+$	0.20±0.01$^+$	13.3±1.7$^+$	11.4±1.2$^+$	9.6±0.6$^+$	10.0
4 (gemfibrozil+HD)	Rats	2.70±0.05$^+$	0.83±0.03$^+$	0.62±0.05$^+$	2.8±0.1$^+$	7.50±0.64$^+$	2.1±0.2$^+$	3.3
	Guinea pigs	2.10±0.2$^+$	2.34±0.1$^+$	0.21±0.05$^+$	15.5±1.5$^+$	12.6±0.5$^+$	12.1±0.4$^+$	9.0

Note. TG, triglycerides; AI, atherogenic index. $p<0.05$ in comparison with the corresponding species *in group 1, $^+$in group 2.

onist benzohexonium (20 mg/kg) had a hypolipidemic effect: it reduces dyslipoproteinemia, fatty infiltration of the liver, and risk of atherosclerotic lesions [6]. Hypolipidemic effect of benzohexonium comparable with that of gemfibrozil can be important in the treatment of patients with AH for normalization of elevated blood pressure and management of dyslipoproteinemia.

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