Arrhythmogenic Effect of Epinephrine during Correction of Dyslipidemia

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In rats with dyslipidemia epinephrine decreased HR and suppressed automaticity of the sinus node. This effect was not eliminated by LBK-149, dibunol, and glutabiance despite normalization of the plasma lipid spectrum. LBK-149 prevented the development of heart rhythm disturbances during epinephrine administration.

Key Words: *dyslipidemia; adrenal arrhythmia*

Disturbances in lipid metabolism lead to LPO activation in tissues and organs and promote the development of metabolic dyshomeostasis [1]. These changes can considerably change the properties of the plasma membrane and cell responses to exogenous events [2-5]. We assumed that dyslipidemia can modulate cell sensitivity to adrenergic stimulation. Our aim was to study the effects of epinephrine on the heart function during experimental dyslipidemia and its therapeutic correction.

MATERIALS AND METHODS

Experiments were carried out on random-bred albino rats of both sexes weighing 180-200 g. Dyslipidemia in experimental rats was modeled by administration of cholesterol (40 mg/kg, *per os* in oil) and vitamin D_2 (25,000 U/kg) for 30 days. During the last 10 days of the experiments, the rats were divided into 4 groups: group 1 comprised controls, groups 2, 3, and 4 rats received LBK-149 (25 mg/kg, 0.12 mmol/kg, intramuscular injections), dibunol (butylated hydroxytoluene, 24 mg/kg, 0.12 mmol/kg, intramuscular injections), and glutabiance (33 mg/kg, 0.12 mmol/kg, *per os*), respectively.

Adrenal arrhythmia was induced on experimental day 30 by intravenous injection of 0.1% epinephrine (0.1 ml per 200 g body weight). Heart rate and conduction disturbances were assessed by ECG recorded in standard lead II.

On days 20 and 30 of dyslipidemia, total cholesterol (TCH), LDL, HDL cholesterol (HDL CH), triglycerides (TG) were measured and atherogenic index (AI) was calculated by the formula:

$$AI = \frac{\text{TCH-HDL CH}}{\text{LDL CH}}$$

RESULTS

On day 20 of the experiment, experimental rats demonstrated disturbances in lipid metabolism: AI, TCH, and LDL increased by 2.3, 1.74, and 2.8 times, respectively (Table 1). On day 30, a negligible decrease in TCH level was noted in group 1 rats, but AI and LDL remained high. The level of TG increased 2-fold compared to the initial value.

In group 2 rats treated with LBK-149, the content of HDL CH was increased 3-fold, which pronouncedly decreased AI (Table 1). The level of LDL decreased 2-fold compared to the control and to the corresponding parameter on experimental day 20. However, the content of TG surpassed the corresponding value in the control group by 1.7 times. Thus, LBK-149 produced a significant hypolipidemic effect and did not prevent (but even slightly potentiated) hypertriglyceridemia.

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TABLE 1. Effect of LBK-149, Dibunol, and Glutabiance on Blood Lipid Spectrum (*M*±*m*)

Group	TCH, mmol/liter	HDL CH, mmol/liter	AI	TG, mmol/liter	LDL, arb. units
Intact	1.02±0.17	0.40±0.02	1.50±0.30	0.56±0.14	6.25±0.15
Dyslipidemia, 20 days	1.77±0.12*	0.39±0.02	3.53±0.40*	0.67±0.16	16.75±1.08*
Group 1	1.49±0.11*+	0.39±0.04	3.02±0.26*	1.22±0.06*+	14.80±2.30*
Group 2	1.39±0.01+	1.24±0.03*+o	0.12±0.01*+o	2.05±0.04*+o	8.75±1.64+o
Group 3	1.80±0.05*o	0.62±0.03*+o	2.01±0.22+o	1.48±0.71*+o	13.00±2.50*
Group 4	1.40±0.14+	0.93±0.09*+o	1.63±0.56+o	0.54±0.15o	8.13±1.88+o

Note. $p<0.05$ compared to: *intact rats; +20-day dyslipidemia; ocontrol (group 1) rats.

On experimental day 30, group 4 rats demonstrated a 2-fold increase in HDL CH in comparison with the control group, while TCH remained virtually unchanged (Table 1). AI, TG, and LDL decreased 2-fold compared to the control values. Thus, glutabiance produced hypotriglyceridemic and hypolipidemic effects in this experimental model.

In group 3 rats, dibunol increased TCH, HDL CH, and TG by 20%, 1.6-fold, and by 21%, respectively (compared to the control group, Table 1). Dibunol decreased AI by 1.5 times. In comparison with other drugs, dibunol produced the lowest hypolipidemic effect.

Thus, all preparations produced hypolipidemic effects of different degrees (LBK-149 was the most potent agent). The decrease of AI was accompanied by a drop in TG level only in rats treated with glutabiance.

In intact rats, adrenal arrhythmia manifested in ventricular tachycardia and extrasystoles (Table 2). In 67% cases, arrhythmia was accompanied by disturbances in atrioventricular conduction. There were no changes in HR both before and after epinephrine injection. During dyslipidemia, epinephrine decreased HR almost 1.5-fold. In this case, there were no significant differences in the incidence of arrhythmias and conduction disturbances in comparison with intact rats.

In group 2 rats, epinephrine decreased HR almost 2-fold. However, no cases of arrhythmia or conduction disturbances were observed in this group. Thus, LBK-149 prevented the development of heart rhythm disturbances, but had no effect on inhibitory action of epinephrine on intrinsic automaticity of the sinus node.

As in intact rats, injection of epinephrine in group 3 animals provoked ventricular tachycardia in 100% cases. Despite almost 2-fold decrease in HR, EGC revealed no disturbances in the atrioventricular conduction. Probably, bradycardia resulted from inhibition of sinus node automaticity. Thus, dibunol significantly prevented atrioventricular conduction disturbances after epinephrine injection.

In group 4, heart rhythm was disturbed in all cases. Epinephrine decreased HR, but atrioventricular conduction was not disturbed.

Therefore, injection of epinephrine during dyslipidemia decreased HR and suppressed automaticity of the sinus node, which was not removed by the test preparations despite normalization of the blood lipid spectrum. In all groups with disturbances in lipid metabolism, epinephrine produced similar changes in HR. This was probably determined by the effect of CH on the viscosity of the lipid bilayer (decreased mobility of fatty acid chains). In this respect, CH acts similarly to cooling [5]. The test preparations LBK-149, glutabiance, and dibunol significantly decreased the incidence of atrioventricular conduction disturbances, but

TABLE 2. Modeling of Adrenal Arrhythmia in Dyslipidemic Rats

Group	*n*	HR		Arrhythmia	Conduction disturbances	Mortality
		initial	after epinephrine			
Intact	6	351±61	360±72	6	4	2
Group 1	10	340±46	200±60o	4	8	4
Group 2	6	320±21	180±13o	0*+	0+	0
Group 3	6	339±16	192±18o	6	0+	4
Group 4	6	345±7	225±7o	6	0+	4

Note. $p<0.05$ compared to: *intact rats; +control (group 1) rats. oNegative chronotropic effect of epinephrine.

only preliminary administration of LBK-149 during 10 days prevented the development of epinephrine-induced arrhythmia.

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