PHARMACOLOGY AND TOXICOLOGY

Correction of Altered β-Glucosidase Activity Induced by the Toxic Effect of Strophanthin K and Modeled Cardiac Decompensation with Cordaron

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Some biochemical mechanisms of the protective effect of cordaron with respect to strophanthin K cardiotoxicity in modeled cardiac failure are experimentally studied in random-bred male albino mice. Strophanthin K is shown to aggravate the disturbances in free and total activity of β-glucosidase and in lysosome membrane permeability in the heart that are characteristic of this pathology. In comparison with the toxic dose of cardiac glycoside, cordaron has an opposite effect on the functional state of the myocardial lysosome system.

Key Words: *strophanthin K; β-glucosidase; heart failure*

The therapeutic effect of cardiac glycosides is known to be limited by high sensitivity to their cardiotoxicity, which often leads to glycoside intoxication, a condition which usually manifests itself in various arrhythmias [1]. Experimental studies have proved cordaron to be one of the most active protectors with respect to strophanthin K (SK) cardiotoxicity [3]. According to published data [5], the heart lysosome system is usually involved in the development of a variety of pathological processes in cardiomyocytes. It seems important to elucidate the possible role of this system in the realization of both the toxic effect of SK and the protective effect of cordaron with respect to the toxicity of this glycoside cardiotonic.

MATERIALS AND METHODS

The experiments were conducted on 66 random-bred male albino rats weighing 160-210 g narcotized with sodium thiopental (40 mg/kg, i.p.). Heart failure (HF) was induced by repeated administration of large (histotoxic) doses of the β-adrenomimetic isoprenaline. The development of HF in experimental animals was verified by the appearance of characteristic hemodynamic disturbances, anatomicohistological changes in viscera, and changes in tolerance for the arrhythmogenic and systemic toxic action of SK [1,3]. To solve the question posed above, we assayed free and total activity of β-glucosidase (BG, EC 3.2.1.21), a heart lysosome enzyme participating in the catabolism of glycosaminoglycans. BG activity was assayed against the background of a minimal arrhythmogenic dose of SK (7.6 mg/kg, preliminarily determined on intact rats [1,3]) administered alone or in combination with a therapeutic dose of cordaron (5 mg/kg) [3]. BG activity was determined spectrophotometrically by the amount of 4-nitrophenol formed in the enzyme reaction [6]. A 0.4% solution of nitrophenyl-β-D-glucopyranoside (Serva) was used as the substrate. Free BG activity was measured in fresh homogenate of myocardium and total activity was assayed in the same homogenate treated with Triton X-100 in a final concentration of 0.1%. The protein content in heart homogenates

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TABLE 1. Effect of Single Intravenous Administration of SK, Cordaron, and Their Combination on BG Activity in the Heart of Intact Rats and Animals with Modeled HF

Experimental conditions	Activity, μmol/min/g protein		Free/total activity, %
	free	total	
Intact rats			
Control	0.1077±0.0024	0.1577±0.0021	68.3±1.0
15 min postinjection:			
SK	0.0365±0.0019*	0.1202±0.0064*	30.6±2.1*
cordaron	0.0539±0.0026*	0.1440±0.0063	37.4±1.1*
SK+cordaron	0.0359±0.0010*	0.1131±0.0044*	31.9±1.1*
30 min postinjection:			
SK	0.1824±0.0031*	0.2085±0.0008*	87.5±1.7*
cordaron	0.0385±0.0014*	0.1199±0.0009*	32.1±1.2*
SK+cordaron	0.1139±0.0039	0.1563±0.0029	72.9±2.4
Heart failure			
Control	0.1681±0.0028*	0.2020±0.0027*	83.3±2.4*
15 min postinjection:			
SK	0.1554±0.0047*	0.1937±0.0039	80.3±3.3
cordaron	0.0760±0.0017*	0.1932±0.0025*	39.3±0.9*
SK+cordaron	0.1260±0.0031*	0.1912±0.0037*	65.9±1.7*
30 min postinjection:			
SK	0.2308±0.0014*	0.2405±0.001*	96.0±0.4*
cordaron	0.0379±0.0026*	0.1541±0.0038*	24.5±1.1*
SK+cordaron	0.1157±0.0025*	0.1751±0.0039*	66.1±1.0*

Note. The data are the mean of 4-8 experiments. *Denotes a reliable difference in comparison with the respective control.

was measured by the biuret method [2]. The experimental data were processed statistically using routine ANOVA tests [4].

RESULTS

The experiments revealed a considerable elevation of BG activity and disturbances in the functional state of lysosome membranes in animals with modeled HF (Table 1). Indeed, analyzing the parameters of hydrolase activity in intact rats and after modeling HF, one can see that the ratio of free activity characterizing lysosome membrane stability was increased by 56.1% with respect to the control values, the total activity being increased by 28.1%. Due to the more marked rise of free BG activity, the ratio of free to total BG activity was increased in comparison with the control values, which attested to labilization of the lysosome membranes in experimental HF.

Administration of a toxic dose of SK to intact animals induced biphasic changes in the functional state of the cardiac lysosome apparatus. At the 15th minute postinjection we observed the stabilizing effect of the preparation on lysosome membranes accompanied by a drop of hydrolase activity, while at the 30th minute the membranes became more labile and the enzyme was released into the cytosol. Under conditions of modeled HF the toxic effect of SK was also accompanied by biphasic changes in BG activity (Table 1). At the 30th min postinjection the ratio of free to total BG activity was markedly increased, attesting to progressive labilization of the lysosome membranes, which is characteristic for HF and probably underlies the reduced tolerance for SK toxicity in this pathology.

These data evidently suggest a real possibility of preventing the development of toxic effects of SK and thereby optimizing its clinical usage through pharmacological regulation of the functional state of lysosome membranes. Cordaron, an effective protector against SK cardiotoxicity [3], exerted a similar inhibiting effect on BG activity and stabilized lysosome membranes both in the intact animals and under conditions of experimental HF. Thus, in healthy rats free BG activity fell 2-fold as soon as 15 min after injection of cordaron, and nearly 3-fold 30 min postinjection. The inhibiting effect of cordaron on BG activity in animals with modeled HF manifested

itself in lowered hydrolase activity, the ratio of free activity of the enzyme — a marker of the stability of lysosome membranes — attaining the level observed in cordaron-treated intact rats.

The combined administration of cordaron with the minimal arrhythmogenic dose of SK to intact rats not only prevented the glycoside-induced elevation of acid hydrolase activity at the 30th min but even restored the functional state of lysosome membranes to the initial level. Under conditions of modeled HF administration of cordaron in combination with a toxic dose of SK also restored the initial ratio of free to total BG activity, which implies in turn stabilization of the lysosome membranes to the initial state. This is clearly due to the opposite effect of cordaron on the levels of free and total BG activity in comparison with the effect of the toxic dose of cardiac glycoside. The mechanism of the inhibiting effect of cordaron on myocardial BG activity and on the stability of lysosome membranes is related to its ability to block lysosome β-adrenoreceptors [5], which may be involved in the regulation of acid hydrolase activity and the functional state of lysosome membranes.

Thus, the changes in BG activity observed against the background of a toxic dose of SK in combination with the protector of glycoside intoxication cordaron clearly prove the reduced lability of lysosome membranes characteristic for HF and disclose the possible biochemical mechanism of the protective effect of pharmacoprotectors with respect to SK cardiotoxicity.

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