EFFECT OF CARDIAC GLYCOSIDES ON RNA CONTENT IN CARDIOREGULATORY STRUCTURES OF THE HIND BRAIN

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Cardiac glycosides (digoxin, strophanthin, isolanide, convallatoxin, etc.), in both therapeutic and toxic doses, interfere with the regulation of protein and nucleic acid metabolism in cardiomyocytes, and this is partly responsible for their therapeutic action and side effects on the heart [1].

Digoxin, a lipid-soluble preparation, is known to penetrate easily into the brain [7]. It is reasonable to suppose that it may have an effect on protein and nucleic acid metabolism also in neurons regulating cardiac activity.

The aim of this investigation was to study the effect of digoxin and its analog, immobilized with the copolymer of N-vinylpyrrolidone with maleic anhydride, mol. wt. 10,000-12,000, on the RNA level in neurons of the nuclei of the vagus nerve and tractus solitarius.

EXPERIMENTAL METHOD

Experiments were carried out on 112 noninbred male albino rats weighing 150-180 g, into which digoxin or its copolymer-fixed analog was injected subcutaneously in the dorsal region, either once 4 h before decapitation, or daily for 6 days, in doses of 0.89 μg/g (conventionally therapeutic) or 8.9 μg/g (toxic) equivalent to 0.1 LD_{50} or LD_{50} respectively (the dose of the immobilized preparation was calculated on the basis of its glycosides content). Control animals (20 experiments) received injections of equal volumes of water.

A block of brain tissue (5 × 5 × 10 mm) excised in the region of the hind brain, was kept for 2 h in Brodsky's fixative and embedded in paraffin wax. Sections 10^{-5} M thick were cut by means of a "Tochmedpribor" rotary microtome and stained by Einarsons' method (the reaction of gallocyanin and chrome alum with nucleic acids). The duration of staining was 48 h at room temperature.

RNA activity was determined on a single-beam MTSFV-1 microspectrocytophotometer with ×40 objective, and with an optical probe 1 μ in diameter at a wavelength of 555 nm.

EXPERIMENTAL RESULTS

The results are given in Table 1. They show that therapeutic and toxic doses of ordinary digoxin, under different experimental conditions (single or long-term administration of the drug) have unequal effects on the RNA level in neurons of cardioregulatory structures.

The RNA level reflects changes in synthesis of intracellular proteins, including membrane proteins which regulate ionic permeability and, consequently, the processes of excitability and conduction in neurons. These proteins are continually being destroyed and their rapid renewal is necessary. For example, the half-life of the membrane enzyme Na^+, K^+-ATPase is about 9 h [6].

Digoxin, fixed to the copolymer, had no significant effect on the RNA level in neurons of the hind brain regulating the work of the heart. We know that high-molecular-weight compounds penetrate with difficulty through the blood-brain barrier [5].

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Table 1. Effect of Digoxin and Its Copolymer-Immobilized Analog on RNA Level in Neurons of Cardioregulatory Structures of Hind Brain

Preparation	Dose, μg/g	Number of injections	Number of injections	RNA content**, optical density units
Control	—	1	10	0,256 (100 %)
		6	10	0,219 (100 %)
Digoxin	0,89	1	20	0,261 (102 %)
		6	20	0,350* (150 %)
Digoxin	8,9	1	20	0,302 (118 %)
		6	20	0,142* (64 %)
Digoxin on copolymer	0,89	1	10	0,253 (98 %)
		6	10	0,226 (103 %)
Digoxin on copolymer	8,9	1	6	0,260 (101 %)
		6	6	0,198 (90 %)

Legend. *$p < 0.05$ (Wilcoxon–Mann–Whitney U test [2]; **) in each experiment RNA content was measured at 10 points, after which the mean value was determined.

It can therefore be postulated that the copolymer, covalently bound with digoxin, limits its penetration into the CNS.

Digoxin, which affects the RNA level in neurons of the cardioregulatory structures, changes the conditons for their functioning. This is important for the manifestation of both the therapeutic and the side effects of this drug on the heart. Changes of this kind may perhaps take place also in neurons in other structures of the CNS, and in particular, this may explain data to the effect that large and small doses of digoxin may have opposite effects on the activity of experimental epileptogenic foci in the hippocampus of rats and frogs [3, 4].

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