Effect of Glialin on Cardiac Ventricular Arrhythmias and Myocardial Conduction System in Dogs

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Intravenous glialin in a dose of 7 mg/kg suppressed the number of ectopic contractions caused by double ligature of the left coronary artery by the method of Harris and almost 2-fold prolonged animal life-span in comparison with the control. The maximum antiarrhythmic effect of glialin developed after 180 min and persisted for 5 h. Glialin injected intravenously (10 mg/kg) after myocardial infarction under conditions of programmed electrical stimulation inhibited conduction of evoked impulse in the atria, Purkinje fibers, and ventricular myocardium and did not modify the effective refractory periods of the atria and ventricles.

Key Words: *class I antiarrhythmic drugs; electrophysiological mechanisms; ECG parameters; arrhythmias*

Allapinin, a lappaconitine alkaloid hydrobromide, is a well-known antiarrhythmic drug, effective for ventricular arrhythmias, paroxysmal atrial fibrillation, and chronic monofocal atrial tachicardia [1]. High toxicity of the drug limits its clinical use despite its advantages in comparison with other antiarrhythmic drugs with similar mechanisms of action. Glialin is a complex of lappaconitine with glycyrrhizic acid in 1:4 molar ratio; it was created at Laboratory of Coordination Chemistry (headed by Prof. Yu. I. Murinov), Institute of Organic Chemistry. Glialin is no less active than allapinin, but is less toxic.

We studied the spectrum of antiarrhythmic activities and electrophysiological effects of glialin.

MATERIALS AND METHODS

Ventricular arrhythmias were induced in 12 dogs (8-15 kg), narcotized with nembutal (30 mg/kg intravenously) by double ligature of the left coronary artery by the method of Harris. The animals were distributed into 3 groups: 1) controls (no treatment); 2) glialin treatment; and 3) allapinin treatment. Antiarrhythmic effects of glialin and allapinin were evaluated 24 h after complete occlusion of the coronary artery in the presence of frequent stable ventricular tachisystole. The drug efficiency was evaluated by recovery of the sinus rhythm. The percentage of ectopic and normal beats was calculated (basal frequency of ectopic beats was taken for 100%) [3].

Electrophysiological mechanisms of action of glialin injected intravenously in doses of 2.5, 5, and 10 mg/kg were studied in 16 dogs (4 of these controls) on day 3 after acute myocardial ischemia using programmed electrical stimulation. The cardiac cycle length (*PP* interval), ECG intervals, and His' bundle electrogram intervals (*PA*, *AH*, *HV*) were measured. Electrostimulation was repeated starting from minute 15 after injection. The effects of glialin on the cardiac conduction system, shown in experiments, were compared with the data for allapinin [2,3].

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TABLE 1. Comparative Study of Glialin (7 mg/kg) and Allapinin (2 mg/kg) in Narcotized Dogs with Experimental Acute Myocardial Ischemia Simulated (*M*±*m*; *n*=4)

Group	Time of extrasystole onset, min	Time of fibrillation onset, min	Time of death, min
1	4.2±0.4 (87.5)	08.1±1.3 (62.5)	15.2±2.8 (62.5)
2	7.9±0.6* (14.3)	20.3±1.4* (28.6)	29.0±3.3* (28.6)
3	10.5±1.8** (33.3)	14.3±2.5 (33.3)	20.2±4.1 (33.3)

Note. Percentage of cases is shown in parentheses; *$p<0.001$, **$p<0.01$ compared to group 1.

In an additional series of experiments the femoral arteries were opened and catheterized in normal dogs under local novocain anesthesia and the effects of glialin on blood pressure, heart rate, and respiration were evaluated during its intravenous drip infusion in doses of 20, 200, 240 μg/kg, and 4 mg/kg. Each dose was studied in a group of 4 animals.

RESULTS

In control experiments 24 h after occlusion of the coronary artery heart rate increased by 20-30% of the initial level, 70-100% of this increase in total heart rate being ectopic beats. Excitability of myocardial fibers returned to normal after injection of glialin in a dose of 7 mg/kg. As a result, ventricular extrasystoles were recorded 8 min after drug injection, while in the control the maximum time of normal rhythm was 4 min. Glialin delayed the development of fibrillation by up to 20 min and almost 2-fold prolonged animal life-span in comparison with the control (Table 1).

Injection of glialin in a dose of 7 mg/kg led to 33-48% suppression of the number of ectopic beats as soon as after 30 min. This was paralleled by recovery of the sinus rhythm. The maximum antiarrhythmic effect developed after 180 min and persisted for 5 h (Table 2).

TABLE 2. Effect of Glialin (7 mg/kg intravenously) on Ectopic Activity of Dog Heart in Experimental Myocardial Infarction

Parameter		Animal No.				*M*±*m*
		1	2	3	4	
Basal	heart rate	182	170	162	172	171.0±5.6
	% ect	98	90	100	96	96.0±2.8
Min after drug injection						
30	heart rate	141	140	143	132	139.0±3.1
	% ect	47	30	38	42	39.3±4.8
90	heart rate	143	150	152	136	145.0±4.5
	% ect	20	10	9	7	11.5±3.6
180	heart rate	151	150	145	139	146.0±3.4
	% ect	4	0	0	0	1.0±1.1
240	heart rate	149	150	149	138	147.0±3.4
	% ect	5	0	0	0	1.25±1.40
360	heart rate	150	153	147	140	148.0±3.6
	% ect	10	0	0	3	3.3±1.9
400	heart rate	147	140	143	132	140.0±4.2
	% ect	15	2	6	6	7.3±2.5
480	heart rate	142	134	142	129	137.0±3.6
	% ect	20	10	15	9	13.5±3.1
540	heart rate	144	137	140	131	138.0±3.6
	% ect	38	30	24	31	30.8±3.9
1000	heart rate	142	140	142	134	140.0±2.2
	% ect	66	79	50	40	59.0±10.1
1200	heart rate	141	140	150	140	143.0±2.8
	% ect	82	90	87	76	84.0±3.9

Note. % ect: percentage of ectopic beats per minute.

TABLE 3. Effects of Different Glialin Doses on ECG and Hisogram (msec) in Dogs with Experimental Myocardial Infarction (*M*±*m*; *n*=4)

Parameter	Control (infarction)	Glialin, mg/kg		
		2.5	5	10
PQ	90±4	95±7	103±8	110±5**
QRS	69±3	72±3	79±3	85±3*
RR	395±14	400±16	398±33	410±63
PP	351±28	354±61	352±43	353±26
QT	236±8	238±9	239±19	239±26
QTc	375±15	381±15	390±21	409±25
PA	20±1	21±5	23±5	25±1**
AH	58±3	58±4	60±7	62±9
HV	26±1	28±2	31±2	34±2**
CL1:1	192±8	180±3	172±4	169±5
Effective refractory period for, msec				
atria	124±2	129±5	130±7	132±5
ventricles	146±7	152±7	149±9	158±10

Note. CL1:1: minimum duration of stimulation cycle, after which 1:1 conduction to ventricles is retained. *p<0.01, **p<0.05 compared to the control.

Hence, glialin is effective in ventricular arrhythmias caused by ligation of the coronary artery in dogs by Harris' method. Glialin in all studied doses had a negligible effect on the sinus node function and did not change heart rate and sinus cycle length (*PP* interval). Glialin in a dose of 10 mg/kg prolonged *PQ* interval by 24% and inhibited pulse conduction via ventricular myocardium (widening of the *QRS* complex). No appreciable changes in the *QT* and *QTc* (*QT* interval corrected by heart rate) were detected. The drug did not modify the effective refractory periods of the atria and ventricles. The *PA* and *HV* intervals, reflecting the conduction via the atria and ventricles, increased, while *AH* interval, characterizing conduction via the atrioventricular node, virtually did not change (*M*±*m*; *n*=4; Table 3), which suggests that glialin can be referred to class IC antiarrhythmic drugs.

In normal dogs (without myocardial ischemia), intravenous drip infusion of glialin in doses of 20, 200, 240 μg/kg, and 4 mg/kg caused a short-term (5-10 sec) negligible elevation of arterial pressure by 4-5 mm Hg with its subsequent normalization (110/70 mm Hg; systolic pressure 110.00± 3.24 mm Hg). ECG parameters remained virtually unchanged. Normal spontaneous respiration was retained (24.0±1.2/min), heart rate and amplitude of cardiac contractions more or less corresponded to the heart rate of intact animals (receiving no drug): 110.0±1.2 bpm.

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