PG. This result is connected with increased transformation of lactate into glucose ($r = 0.94$; $p < 0.001$). Meanwhile PG inhibited tissue protein breakdown in rats.

The writers showed previously that ligation of the coronary artery leads to a sharp fall in the tissue glycogen level of rats [3]. However, after injection of $PGF_{2\alpha}$, the glycogen concentrations in the liver and heart and skeletal muscles were almost identical, normal in value, and higher than in rats with MI not receiving PG, by 9.1, 5.2, and 3.9 times, respectively (3rd day), by 3.4, 2.7, and 3.2 times (10th day), and by 2.7, 2.0, and 2.6 times, respectively (20th day of the experiment). Consequently, in rats with MI, glycogenolysis is intensified under the influence of $PGF_{2\alpha}$, and this has a marked cardioprotective action with respect to glycogen.

Further confirmation of the above was obtained by the study of G6Pase and F-1.6-DPase activity (Fig. 1): the increase in activity of these enzymes was greater in rats with MI due to coronary occlusion, and receiving PG injections. This reflects the higher rate of transformation of noncarbohydrate compounds into glucose.

The authors are grateful to S. D. Varfolomeev and to A. T. Mevkh for advice.

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EFFECT OF FLUORINE ON CARDIAC ARRHYTHMIAS IN RATS

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UDC 616.12-008.318.02:615.31:546.16]-092.9-07

KEY WORDS: calcium chloride arrhythmias; fluorine; blockade; inward calcium current.

Since hyperactivation of cardiomyocytes and the development of cardiac arrhythmias are linked with intensive inflow of Ca^{++}, blockers of slow Ca channels have been found to be effective antiarrhythmic agents [2, 6, 7]. Considering data showing that intracellular injection of fluorine ions induces blockade of the inward Ca current in the somatic membrane of neurons [5, 8], it was decided to test the antiarrhythmic activity of fluorine in experiments with a calcium chloride model of cardiac arrhythmia.

EXPERIMENTAL METHOD

Experiments were carried out on 58 control and 56 experimental noninbred male rats weighing 260-350 g. Throughout the experiment the animals were kept in the animal house of the Institute on a standard diet (pellet food, milk products). Sodium fluoride was used in tablet

Research Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR G. N. Kryzhanovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 107, No. 3, pp. 281-283, March, 1989. Original article submitted May 15, 1988.

 0007-4888/89/0003-0302$12.50

form (Natrium fluoratum, Poland), the tablets being ground and added to the drinking water of the experimental animals; a solution of chemically pure sodium fluoride also was used to exclude any effect of the materials added to give the tablets their shape. The aim of the investigation included determining the effect of different concentrations of fluorine and the duration of its administration. Accordingly, the animals of series I and II received sodium fluoride with their drinking water in a concentration of 2 mg/liter (0.90 mg/liter calculated as the anion) for 1 month (for the animals of series II, tablets of Natrium fluoratum were used), the animals of series III received sodium fluoride in a concentration of 5 mg/liter (2.26 mg/liter calculated as the anion), those of series V – in a concentration of 11 mg/liter (5 mg/liter calculated as the anion), and animals of series IV – in a concentration of 2 mg/liter for 2 months. There was no limitation on the quantity of fluorided water which could be drunk. The fluorine concentration in the tap water was 0.3 mg/liter.

Cardiac arrhythmia was induced by intravenous injection of calcium chloride (0.14-0.20 ml of a 10% solution/100 g body weight) for 30 sec into rats anesthetized with urethane (1.6 g/kg, intraperitoneally). The action of calcium chloride was estimated from data of the ECG, which was recorded in two standard leads (II and III) on an "Elkar-4" electrocardiograph.

EXPERIMENTAL RESULTS

Preliminary experiments showed that long-term (for 1 month) consumption of sodium flouride by the animals with their drinking water in a concentration of 2 mg/liter did not affect the heart rate (Table 1, series I and II). Injection of calcium chloride induced disturbances of the cardiac rhythm in all animals not receiving sodium flouride; they were recorded, moreover, as early as the 12th second of injection of calcium chloride, and 60% of the animals died after 60-90 sec. In rats receiving fluoride (2 mg/liter) arrhythmias developed after twice as long a delay, and the frequency of ventricular tachycardias and their duration were less than in the control animals (by 1.5 and 2.9 times, respectively). The rats died 2.4 times less frequently. Ventricular fibrillation developed in seven of the 10 control rats not receiving fluoride but in only one of the 12 rats receiving it. A similar antiarrhythmic effect was observed when sodium flouride was given in tablet form (Table 1, series II). Only two rats receiving fluorine developed ventricular fibrillation, compared wiht 10 of 22 rats in the control group.

Consumption of water with an increased sodium fluoride concentration (5 mg/liter) induced arrhythmias in two of the 11 animals (atrioventricular blockade of the II degree and sinus arrhythmia). Meanwhile it had a marked antiarrhythmic action when calcium chloride was injected into the animals of this series (Table 1, series III): arrhythmias developed after twice as long a delay in animals receiving this dose of fluoride than in control rats not receiving fluoride, and death was observed in 18% of cases (50% in the control animals). Ventricular fibrillation was observed in two of 10 animals receiving fluoride, and was of relatively short duration (on average 10 sec), whereas in the control animals fibrillation occurred in five of 10 cases and its average duration was 56 sec.

Animals of series IV of the experimental group received sodium flouride with the drinking water in a concentration of 2 mg/liter for 2 months. Five (33%) of the 15 rats had sinus arrhythmia. In animals receiving this dose of fluorine, calcium chloride injection induced disturbances of rhythm just as frequently and just as severely as in animals not receiving fluorine.

Animals receiving sodium flouride in a much larger dose (11 mg/liter) for 1 month died in 100% of cases after injection of calcium chloride; control animals not receiving fluorine died in 20% of cases. Ventricular tachycardia was observed in all rats receiving fluorine (in five of the 10 control rats) and eight of the 10 experimental rats (but none of the control animals) developed ventricular fibrillation (Table 1, series V).

The results of these investigations thus show that long-term (for 1 month) consumption of sodium flouride with the drinking water in a concentration of 2 mg/liter had a marked antiarrhythmic action, and greatly reduced the severity of calcium chloride arrhythmias in rats. This effect was observed to a lesser degree in rats receiving fluorine in a concentration of 5 mg/liter. With more prolonged fluorine consumption (2 months, 2 mg/liter) its positive effect on calcium chloride arrhythmias was reduced. Increasing the dose of sodium chloride to 11 mg/liter, consumed for 1 month, greatly aggravated the severity of the calcium chloride arrhythmias.

TABLE 1. Action of Sodium Fluoride (NaF) on Severity of Calcium Chloride ($CaCl_2$) Arrhythmias in Rats (M ± m)

Series of experiments	Dose and duration of consumption of NaF	Group and number of animals	Weight of animals, g	Number of cardiac contractions per minute before injection of $CaCl_2$	Time of onset of arrhythmias after beginning of $CaCl_2$ injection, sec	Number of lethal arrhythmias after injection of $CaCl_2$, %	Arrhythmias			
							ventricular tachycardia		ventricular fibrillation	
							frequency of development, %	duration, sec	frequency of development, %	duration, sec
I	2 mg/liter 1 month	Control ($n=10$)	328 ± 10	348 ± 21	12,3 ± 1,8	60 ± 16	90,0 ± 10,0	9,0 ± 2,2	70,0 ± 15,3	24,7 ± 6,3
		Experiment ($n=12$)	314 + 13	354 ± 29	23,8 ± 2,9[a]	25 ± 13	58,3 ± 14,9	3,1 ± 1,3[a]	8,3 ± 0,1[d]	16 ± 1,4[d]
II	2 mg/liter 1 month	Control ($n=22$)	286 ± 6	375 ± 15	12,3 ± 2,0	36 ± 10	77,3 ± 8,9	7,9 ± 0,9	45,5 ± 10,6	15,0 ± 2,9
		Experiment ($n=14$)	283 ± 7	358 ± 19	18,2 ± 1,7[a]	12 ± 9	42,8 ± 13,2[a]	3,6 ± 1,0[b]	14,2 ± 0,1[a]	8,5 ± 1,3[d]
III	5 mg/liter 1 month	Control ($n=10$)	290 ± 6	339 ± 17	10,4 ± 2,4	50 ± 16	70,0 ± 14,5	4,8 ± 0,8	50,0 ± 16,0	55,6 ± 16,[d]
		Experiment ($n=10$)	304 ± 6	386 ± 35	19,9 ± 2,8[a]	18 ± 12,	50,0 ± 15,6	3,6 ± 1,7	20,0 ± 14,3	9,5 ± 1,8
IV	2 mg/liter 2 months	Control ($n=15$)	332 ± 14	374 ± 30	10,1 ± 1,9	67 ± 13	73,3 ± 1,8	7,8 ± 1,3	60,0 ± 13,1	31,8 ± 4,4
		Experiment ($n=15$)	330 ± 7	338 ± 23	11,7 ± 1,4	73 ± 12	80,0 ± 10,7	9,6 ± 2,1	73,3 ± 11,8	26,5 ± 2,2
V	1 mg/liter 1 month	Control ($n=10$)	272 ± 4	315 ± 6	17,7 ± 4,6	20 ± 13	50,0 ± 15,8	3,0 ± 0,7	—	—
		Experiment ($n=10$)	275 ± 5	323 ± 9	12,2 ± 1,4	100 ± 0[c]	100,0 ± 0,0[b]	10,8 ± 2,6[b]	80,0 ± 12,6[c]	20,6 ± 5,9[c]

Legend. Significance of difference (p) calculated by comparison with corresponding parameters for control animals: a) $p < 0.05$, b) $p < 0.02$, c) $p < 0.01$, d) $p < 0.001$.

It can be postulated that prevention of arrhythmias induced by calcium chloride by sodium fluoride is linked with blockade by fluorine of the inward Ca current [5, 8]. At the same time, we know [4] that fluorine itself can cause activation of adenylate cyclase, which leads to intensification of cellular activity. Potentiation of the arrhythmogenic effects of calcium chloride by the action of large doses of fluorine can probably be linked with this mechanism. Toxic effects of fluorine, used in high doses, also may probably be connected with its inhibitory effect on many enzymes in the body [3]. In hyperfluoridation changes take place in protein, fat, carbohydrate, and mineral metabolism and RNA metabolism is disturbed [1]. These toxic effects are cumulative in the case of chronic fluorine intake in high concentrations.

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