maker mechanism, whose function is closely bound with the state of metabolism of the neuron [1, 3].

The problem of whether intraneuronal reverberative relations apply in the genesis of burst activity during paroxysmal depolarization shifts, and whether they are involved in the formation of epileptiform activity of neurons require further study.

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EFFECT OF THE CALCIUM CHANNEL BLOCKER RYODIPINE ON FOCAL AND GENERALIZED EPILEPTIC ACTIVITY

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An important role in the mechanisms of neuronal epileptic activity is ascribed to a change in Ca^{++} homeostasis [4-6]. A fall in the Ca^{++} concentration in the extracellular space, which always procedes an epileptic discharge, and entry of Ca^{++} into neurons through the cytoplasmic membrane are among the mechanisms of neuronal hyperactivation and they exert a considerable influence on the formation and intensity of discharges arising within an epileptic focus [10, 11]. Since voltage-dependent calcium channels are the main pathway of entry of Ca^{++} inside the cell, their blockade plays an important role in the termination of epileptic activity [7-9].

The aim of this investigation was to study the effect of ryodipine [foridon; 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(o-difluoromethoxyphenyl)-1,4-dihydropyridine], a new calcium channel blocker (the preparation was synthesized at the Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR) [3], on focal and generalized epileptic activity (EA). Foridon, as a Ca^{++}-antagonist, has been used in the treatment of hypertension [3]. During the study of its effect on the CNS, both a sedative component of its action and an anticonvulsive effect, when administered perorally [1], have been described.

EXPERIMENTAL METHOD

Experiments were carried out on 102 male Wistar rats weighing 200-220 g. To create a model of focal EA, holes were drilled (2 × 4 mm) 24 h before the experiment, by the method described

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TABLE 1. Effect of Ryodipine on Focal EA Induced by Application of Penicillin (20,000 IU/ml) to the Rat Cerebral Cortex (M ± m)

Group of animals	Number of animals	Before injection			After injection (1-30 min)			Number of SD during life of focus	Duration of focus, min
		number of PD per minute	amplitude of PD, mV	number of SD per minute	number of PD per minute	amplitude of PD, mV	number of SD per minute		
1. (Control): physiological saline	7	12,0±0,7	0,94±0,05	0,33±0,04	11,0±0,7	0,83±0,06	0,24±0,03	26,0±3,1	135,0±5,0
2. (control): DMSO	13	13,0±0,7	0,93±0,05	0,32±0,03	12,0±0,9	0,82±0,07	0,24±0,03	23,0±5,2	130,0±6,8
3. Ryodipine 1 mg/kg	7/7	16,0±2,8	0,96±0,09	0,30±0,03	7,0±2,0*	0,48±0,14*	0,11±0,07*	12,0±2,8*	98,0±5,7*
4. Ryodipine, 2 mg/kg	8/7	13,0±2,2	0,92±0,07	0,19±0,03	8,0±1,9	0,40±0,09*	0,01±0,01*	7,0±1,3*	94,0±9,7*
5. Ryodipine, 5 mg/kg	7/7	14,0±1,6	0,94±0,09	0,34±0,05	7,0±1,9*	0,76±0,19	0,04±0,03*	13,0±2,9*	100,0±5,6*

Legend. Numerator – number of animals in which ryodipine induced suppression of EA; denominator – total number of animals in group. *$p < 0.05$; significant difference compared with corresponding parameter in column "before injection" or with control.

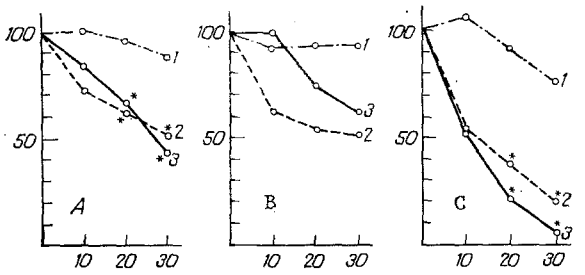

Fig. 1. Effect of ryodipine on amplitude (a) and number of PD (b) and SD (c) in epileptogenic focus induced by application of penicillin (20,000 IU/ml). Abscissa, time after injection of ryodipine (in min); ordinate, parameters tested (in %; initial values before injection of ryodipine taken as 100%). 1) Control (DMSO); 2, 3) ryodipine in doses of 1 and 2 mg/kg, respectively.

previously [2], in the animal's skull above symmetrically opposite regions of the sensomotor cortex, and monopolar silver cortical electrodes were applied to derive electrical activity from these areas of the cortex (the ECoG). Foci of EA were created by applying filter paper soaked in a solution of benzylpenicillin sodium in a concentration of 20,000 IU/ml. The EcoG was recorded on an EEG 8S encephalograph (Hungary) in unrestrained animals. Ryodipine was dissolved in 50% dimethyl sulfoxide (DMSO) and injected intraperitoneally in doses of 1, 2, and 5 mg/kg against the background of sustained generation of seizure (ictal) discharges in the focus (series I) and in a dose of 2 mg/kg 30 min before creation of foci of EA (series II). Amplitude-frequency characteristics were determined and the duration of existence of the epileptic foci measured. Generalized EA was created by intraperitoneal injection of metrazol in a dose of 60 mg/kg. The observed effects were recorded visually for 15-60 min. The intensity of the seizures, the latent periods of the first convulsive manifestations, and of seizures (the animal falling on its side), and mortality were determined.

EXPERIMENTAL RESULTS

Application of penicillin to the sensomotor cortex led to the appearance of focal EA after 2-7 min; separate peak (interictal) discharges (PD) appeared, and their amplitude increased gradually; after 6-15 min seizure (ictal) discharges (SD) appeared, and after 25-35 min the stage of marked seizure activity began, characterized by the regular appearance of SD, and lasting 30-40 min, after which the manifestations of SD became less frequent and the frequency and amplitude of the PD also decreased. The duration of the foci of EA from the time of application of penicillin until total disappearance of the EA was 128-167 min. During this time 28-50 SD were recorded. In animals of the control groups (Table 1; groups 1 and 2) 25-40 min after penicillin application, against the background of sustained SD generation, injection of physiological saline and of DMSO had no effect on the character of EA.

Injection of ryodipine in a dose of 1 mg/kg in the stage of marked seizure activity caused suppression of EA in the focus in 100% of cases, as shown by reduction of the amplitude and frequency of appearance of SD (by 63%). The total number of SD throughout the period of existence of the foci of EA in the animals of this group was reduced by 52%, and the life of the focus by 25% (Table 1; group 3). An increase in the dose of ryodipine to 2 mg/kg also caused suppression of EA in the focus in 87% of cases. The amplitude and frequency of appearance of PD fell by 37 and 57%, respectively, and the frequency of appearance of SD by 95%. Thus the effect of suppression of SD under the influence of ryodipine was more marked in a dose of 2 mg/kg. The duration of the epileptic foci and also the total number of SD were less than in animals of the control group (Table 1; groups 2 and 4).

A further increase in the dose of ryodipine to 5 mg/kg was not accompanied by stronger suppression of EA than was observed with the doses used previously (Table 1; group 5). In animals of all groups the most marked antiepileptic effect was observed 20-30 min after injection of ryodipine (Fig. 1).

In the next series of experiments ryodipine was injected 30 min before creation of the foci of EA. Preliminary injection of ryodipine increased the latent period of onset of SD in the focus by 36%, increased the total number of SD by 65% without any change in their duration, and reduced by 21% the duration of the focus, but had no effect on the latent period of appearance of the first PD and the frequency of their generation throughout the life of the focus (Table 2).

Investigations of the effect of ryodipine on generalized EA induced by intraperitoneal injection of metrazol (60 mg/kg) showed that injection of ryodipine in a dose of 2 mg/kg 30 min before injection of metrazol caused a significant increase in the latent period of

TABLE 2. Injection of Ryodipine (2 mg/kg) 30 min before Creation of Focus of EA (M ± m)

Group and number (n) of animals	Latent period 1, sec	Number of PD per minute			Latent period 2, sec	Total number of SD	Mean duration of SD, sec	Duration of focus, min
		after 30 min	after 60 min	after 90 min				
Control n = 8	3,0±0,2	7,0±1,5	9,0±1,4	6,0±1,7	11,0±1,0	26,0±1,7	26,0±1,1	125,0±3,9
Experimental n = 8	4,0±0,1	9,0±1,6	12,0±2,1	8,0±2,0	15,0±0,9*	9,0±1,6*	25,0±1,1	99,0±5,1*

Legend. Latent period 1 denotes time from application of penicillin to appearance of first PD; latent period 2 denotes time from application of penicillin to appearance of first SD. *$p < 0.01$: significant difference compared with corresponding parameter in control group.

the first seizure manifestation (from 50.7 ± 2.8 sec in the control to 82.8 ± 6.0 sec in the experiment; $p < 0.001$) and delayed the development of generalized clonicotonic convulsions (from 73.7 ± 3.5 sec in the control to 136.6 ± 6.3 sec in the experiment; $p < 0.001$; $n = 30$).

The results of these investigations thus demonstrate that in the majority of animals ryodipine caused suppression of focal and generalized EA. These results are in agreement with those obtained by other workers studying the antiepileptic effects of Ca^{++} antagonists [2, 8, 12, 14, 15]. Meanwhile these effects of the calcium channel blockers, including ryodipine, may be linked with their hypotensive action. This factor was not always taken into consideration by other workers [9, 13]. To test this hypothesis a series of experiments was carried out to study the action of ryodipine on EA in a focus with simultaneous recording of pressure by means of a tail plethysmograph. For this purpose the animals were placed in Plexiglas cages, limiting their movements, and the initial pressure level was recorded. The animals were taken out of the cages for intraperitoneal injection of ryodipine. As the control experiment showed, injection of ryodipine into intact rats in a dose of 1 mg/kg caused a small and not significant fall in pressure (by 7-14% in four rats), and after injection of 5 mg/kg a greater fall of pressure was observed (by 25% in three rats and by 47% in one rat). This fall was most marked during the first 3-10 min after injection.

After application of penicillin, through a special hole in the cage, without removing the animals, the appearance of EA was recorded in the focus and the pressure was increased by 5-45 mm Hg in all the six animals studied. Injection of ryodipine against this background lowered the pressure to its initial level. Suppression of EA in the focus did not correlate with the time or degree of fall of pressure. This conclusion is in agreement with data according to which the antiepileptic effect of ryodipine in doses of 1 and 5 mg/kg is virtually the same, despite the longer fall of pressure with a dose of 5 mg/kg. The most marked antiepileptic effect of ryodipine, moreover, was observed not during the first few minutes after its injection, when the greatest fall of pressure was observed, but after 20-30 min, i.e., during its recovery period. Nevertheless, the question of the possible effect of the fall of pressure under the influence of ryodipine on activity of the epileptogenic focus requires further investigation.

The new Ca^{++} antagonist ryodipine thus has an antiepileptic action, suppressing EA in foci and lengthening the latent period of onset of generalized seizure responses.

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ROLE OF LIPID PEROXIDATION IN REGRESSION OF THE HYPERTROPHIED HEART

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During adaptation to periodic hypoxia under pressure chamber conditions, nucleic acid and protein synthesis is activated, with the result that hypertrophy of the right ventricle (due to pulmonary hypertension) and, to a lesser degree, hypertrophy of the left ventricle (due to an increase in cardiac output) develops [5]. After the end of exposure to hypoxia, regression of the hypertrophied heart quickly takes place [4]. However, the concrete molecular mechanisms of disassembly of the myocardial structures have not been studied. In our view, one factor which may play a role in this process is lipid peroxidation (LPO), which is involved in destruction and disassembly of biological membranes [1, 2].

It was accordingly decided to compare the dynamics of regression of the hypertrophied heart with activity of LPO, estimated as concentrations of diene conjugates.

EXPERIMENTAL METHOD

Male Wistar rats weighing initially 185 ± 6 g were used. The rats were adapted to periodic high-altitude hypoxia by "raising" them to an altitude, increasing by 1000 m daily up to a peak value of 7000 m, in a hypobaric pressure chamber. The animals were kept at this "altitude" for 18 days (6 days a week) for 6 h daily. At the end of the period of adaptation the rats weighed 232 ± 9 g, whereas animals kept under standard animal house conditions (control) weighed 281 ± 8 g. Altogether five groups of rats were studied: control (without adaptation), 1, 3, and 7 days after the last session of hypoxia, and 7 days after hypoxia, during which period the rats were given ionol by intraperitoneal injection in a dose of 50 mg/kg on the 1st, 3rd, and 5th days.

TABLE 1. Weight of Heart and Its Divisions and Content of Hemoproteins in Them after Adaptation and during Regression (M ± m)

Parameter	Control (without adaptation)	Adaptation	Regression		
			3 days	7 days	7 days + ionol
Relative weight of heart, g/kg body weight	2,62±0,04	3,77±0,17***	3,23±0,08***	2,75±0,06	3,28±0,14**
Relative weight, g/kg body weight					
of right ventricle	0,74±0,02	1,46±0,08***	1,06±0,03***	0,77±0,06	1,00±0,05***
of left ventricle	1,88±0,02	2,31±0,11**	2,17±0,08*	1,98±0,04*	2,27±0,11***
Myoglobin concentration, mg/g					
in right ventricle	0,27±0,02	0,35±0,05*	0,32±0,06	0,30±0,06	0,33±0,33*
in left ventricle	0,38±0,05	0,46±0,06	0,42±0,04	0,37±0,05	0,39±0,05
Hemoglobin concentration, mg/g					
in right ventricle	0,16±0,02	0,29±0,05**	0,20±0,04	0,18±0,05	0,25±0,04*
in left ventricle	0,18±0,02	0,30±0,05*	0,22±0,05	0,21±0,03	0,29±0,05*

Legend. ***p < 0.01, **p < 0.02, *p < 0.05.

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