The results on accumulation of [^{3}H]-GABA in the various brain structures under the influence of alcohol obtained in these experiments are difficult to compare with data in the literature on the content of endogenous GABA in the brain of animals receiving alcohol, chiefly because in investigations of this kind the GABA content was determined not in individual brain structures, but mainly in the cerebral hemispheres and cerebellum. Furthermore, data on the GABA content in the brain during alcoholization are extremely contradictory in character. They range from an increase in its level [8] to a decrease, or to no change [5].

At the same time it will be evident that significant factors affecting the GABA content in brain structures are the method of administration of the alcohol (compulsory or voluntary consumption under free choice conditions) and the duration of chronic exposure.

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EFFECT OF PANTOGAM, NICOTINAMIDE, AND PHENAZEPAM ON SEIZURE ACTIVITY

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Pantogam, the calcium salt of D-homopantothenic acid (synthesized in the "Vitaminy" Scientific Production Department by V. M. Kopelevich, T. D. Marieva, and V. I. Gunar), is known to possess antiepileptic activity [1, 4]. It has also been shown that nicotinamide (the hypothetical endogenous ligand of benzodiazepine receptors [12]) can inhibit some forms of epileptic activity [5, 6]. Phenazepam is one of the most effective drugs with an anticonvulsant action [2].

In the investigation described below a comparative study was made of the effects of pantogam, nicotinamide, phenazepam, and combinations of them on generalized seizure activity.

EXPERIMENTAL METHOD

Noninbred albino mice weighing 18-24 g were used. Clonic seizures were induced by subcutaneous injection of metrazol in a dose of 60-70 mg/kg body weight, and clonico-tonic convulsions were induced by intraperitoneal injection of metrazol in a dose of 80-100 mg/kg

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TABLE 1. Effect of Pantogam and Nicotinamide on Clonico-Tonic and Clonic Convulsions (M ± m)

Experimental conditions	Dose, mg/kg	Number of animals	Latent period of first convulsions, sec	Intensity of convulsion, points	Mortality, %
			Clonico-tonic convulsions		
Control (metrazol)	80	30	43,8±1,4	3,6±0,09	57,1±9,5
Pantogam	500	20	92,8±6,2*	2,1±0,2*	10,0±6,9*
	1000	10	120,5±9,0*	1,6±0,2*	0
Nicotinamide	250	10	61,6±3,2*	3,7±0,2	60,0±16,3
	500	50	116,1±7,0*	3,5±0,2	56,0±7,1
	1000	10	187,7±8,7*	1,0±0,0*	0
Pantogam + nicotinamide	250 + 250	10	104,0±2,4*	2,4±0,2*	0
The same	250 + 500	15	157,3±6,2*	1,8±0,1*	0
			Clonic convulsions		
Control (metrazol)	60	25	161±5,6	2,0	0
Pantogam	100	10	218,5±19,8*	1,6±0,2	0
	250	11	263,2±21,7*	1,6±0,2	0
	500	10	272,0±19,8*	1,4±0,2‡	0
Pantogam + nicotinamide	100 + 250	20	295,0±32,4*	1,4±0,2†	0

Legend. *P < 0.001, †P < 0.01, ‡P < 0.05 compared with control.

body weight. The intensity of the seizures was estimated in points according to the scale: 0) no seizure response; 1 point) paroxysmal twitches; 2 points) clonic convulsions; 3 points) marked clonico-tonic convulsions with the animals falling on their side and with a distinct phase of tonic extension; 4 points) fatal clonico-tonic convulsions. The number of animals with seizures, the latent periods of the first manifestations of seizures, the latent period of marked seizures (animals falling on their side) and of seizures of maximal intensity, the frequency of clonic convulsions, and mortality also were determined. Pantogam and nicotinamide were injected in 0.1-0.3 ml of 0.9% NaCl solution 1 h and 15 min before injection of metrazol. Phenazepam (15 min before injection of metrazol) was injected in a Tween emulsion of isotonic NaCl solution. All three preparations were injected intraperitoneally and control animals received 0.9% NaCl solution. The significance of differences was assessed by the Student–Fisher t test.

EXPERIMENTAL RESULTS

Pantogam, given in a dose of 500 mg/kg to mice with clonic-tonic convulsions, doubled the latent period of the first manifestations of convulsions, considerably weakened the intensity of the seizure, and reduced the mortality (Table 1). Increasing the dose of pantogam to 1000 mg/kg completely prevented death of the animals. In this dose pantogam reduced the severity of the seizure by a greater degree than in a dose of 500 mg/kg, it abolished the phase of tonic convulsions, and it weakened the clonic convulsions. In animals with experimental clonic convulsions pantogam, in doses of 100-500 mg/kg, lengthened the latent period of the first convulsions, and in a dose of 500 mg/kg it also reduced their intensity. When pantogam was given in doses of 500-1000 mg/kg, single slight twitches were observed.

Nicotinamide, in doses of 250-500 mg/kg, lengthened the latent period of the first convulsions without having any significant effect on the severity of the seizures and mortality (Table 1). Increasing the dose of nicotinamide to 1000 mg/kg prevented death of the animals and the development of clonico-tonic convulsions. Only single twitches were observed. The latent period of the first manifestations of convulsions was increased to 3 h after injection of nicotinamide in a dose of 1000 mg/kg. The effectiveness of nicotinamide depended on the time of its injection. Maximal delay of the seizures was observed 15 min after injection of nicotinamide (for a dose of 500 mg/kg).

Combined administration of pantogam and nicotinamide in a dose of 250 mg/kg of each in animals with experimental clonico-tonic convulsions had the same anticonvulsant action as pantogam alone in a dose of 500 mg/kg, and it reduced the intensity of the convulsions much

TABLE 2. Effect of Pantogam and Phenazepam on Clonico-Tonic Convulsions (M ± m)

Experimental conditions	Dose, mg/kg	Number of animals	Latent period of first convulsions, sec	Latent period of marked convulsions, sec	Number of convulsions during first 15 min	Intensity of convulsions, points
Control (metrazol)	100	30	36,0±0,6	42,6±1,3	56,2±1,4	4,0
Phenazepam	0,1	25	69,2±2,5*	87,5±5,1*	24,9±2,4*	2,0 †
Pantogam + phenazepam	100 0,1	20	89,6±5,3*	115,7±11,4*	10,1±0,9*	1,7±0,009*
"	250 0,1	35	85,4±4,3*	118,6±10,1*	9,1±0,09*	1,7±0,08*
"	500 0,1	15	148,0±6,0*	144,4±1,4*	9,7±1,6*	1,5±0,1*
"	250	10	56,3±3,4*	67,8±6,5*	36,7±4,4*	3,0±0,3*
"	250 0,2	10	167,0±9,3*	205,0±11,8*	7,7±0,9*	1,3±0,2*

Legend. *P < 0.001, †P < 0.01 compared with control.

more effectively than nicotinamide in a dose of 500 mg/kg (P < 0.01, see Table 1). Combined injection of pantogam and nicotinamide in doses of 250 and 500 mg/kg respectively weakened the convulsions, just as after injection of pantogam in a dose of 1000 mg/kg, and it lengthened the latent period of the first manifestations of convulsions by a greater degree than pantogam alone in the above-mentioned dose (P < 0.05). On a model of clonic convulsions pantogam, in a dose of 100 mg/kg, combined with nicotinamide in a dose of 250 mg/kg, had the same effect as pantogam alone in a dose of 500 mg/kg (Table 1).

Phenazepam in a dose of 1.4 mg/kg completely prevented convulsions even when high doses of metrazol (100 mg/kg), causing death in 100% of cases, were used. Reducing the dose of phenazepam to 0.7 mg/kg did not prevent the onset of convulsions, but these were weak (intensity not more than 1 point). In doses of 0.1-0.2 mg/kg phenazepam prevented death of the animals and weakened the manifestations of convulsions (Table 2).

After the combined injection of pantogam and phenazepam a stronger anticonvulsant effect was obtained than when they were given separately (Table 2). Pantogam, for instance, starting with a dose of 100 mg/kg combined with phenazepam in a dose of 0.1 mg/kg, increased the latent periods of the first manifestations of convulsions and the latent periods of marked convulsions (P < 0.01) and also reduced the frequency (P < 0.001) and severity of the convulsions (P < 0.01) compared with these same parameters when phenazepam alone was given in a dose of 0.1 mg/kg. In the same way, combined administration of pantogam and phenazepam in doses of 500 and 0.1 mg/kg respectively had a stronger anticonvulsant action (P < 0,02) than pantogam and phenazepam when given separately in the above-mentioned doses.

These experiments thus showed that pantogam has very marked anticonvulsant properties, as the results of clinical studies have confirmed [8, 9, 11]. Nicotinamide in relatively large doses has anticonvulsant activity not only against single epileptic foci and groups of such foci in the cerebral cortex [5, 6], but also against generalized convulsions induced by metrazol. Phenazepam has high anticonvulsant activity. When these substances were used in combination, their anticonvulsant effect was stronger still and could be achieved with a reduction in the doses of the individual drugs compared with those when given separately. The data on the mechanisms of action of GABA and diazepines are evidence that GABA exerts its action through interaction with GABA receptors and it is regulated by benzodiazepine receptors through their binding of benzodiazepines [13]. It can accordingly be postulated that the effects of the combined administration of phenazepam or nicotinamide with pantogam are the result of true potentiation of the action of these compounds.

Vitamin preparations in increased doses and pantogam thus possess anticonvulsant activity. This raises the question of the use of vitamin preparations (α-tocopherol [10], pyridoxal-5-phosphate [3, 7], nicotinamide [5, 6]) and pantogam in the combined treatment of epilepsy together with phenazepam and other anticonvulsants. It can be tentatively suggested that such combined treatment would not only give an anticonvulsant effect, but it would also improve the nutrition and structural metabolism of the brain, and this would be a matter of great importance for the prevention of its disorganization and degradation, that are so particularly characteristic of chronic pathological processes.

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ACTION OF PYRAZIDOLE ON EFFECTS OF SEROTONIN AND PHENYLETHYLAMINE

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KEY WORDS: pyrazidole; 5-hydroxytryptophan; phenylethylamine.

The antidepressant pyrazidole differs from other known antidepressants in the spectrum of its psychopharmacologic activity [1].

The special features of pharmacologic activity of pyrazidole are determined primarily by its different effects on different brain monoamines. Biochemical studies have shown that pyrazidole inhibits oxidative deamination of serotonin but has virtually no effect on deamination of phenylethylamine (PEA) in the brain [1, 2]. The central serotonin-potentiating action of pyrazidole was manifested as potentiation of the convulsant activity of 5-hydroxytryptophan (5-HTP) [1].

In this paper new data are given in the antiserotonin action of pyrazidole and its action on the effects of PEA.

EXPERIMENTAL METHOD

The effect of pyrazidole on central serotoninergic structures was studied on mice by the use of 5-HTP by the method in [3]. Pyrazidole and, for comparison, imipramine were given internally in different doses 60 min before intraperitoneal injection of 5-HTP in a dose of 300 mg/kg. The number of head twitches of each mouse was determined in the course of 1 min 25 min after injection of 5-HTP. In a separate series of experiments the rectal temperature was measured 30 min after injection of 5-HTP, against the background of pyrazidole and imipramine.

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