incubation of ^{14}C-GABA with BM of myometrial cells in the presence of ^{3}H-flunitrazepam significant changes were observed in the binding parameters of the labeled ligands. Under these conditions K_d of the GABA-receptor complex was 60 ± 7 nM. The affinity of the benzodiazepine receptor sites also was increased (K_d = 11 ± 4 nM). The number of binding sites of the labeled ligands in the PM of the cells was virtually unchanged (Figs. 1 and 2). The changes we found indicate that specific binding sites of ^{14}C-GABA and ^{3}H-flunitrazepam are coupled, and evidently in the same way as the GABA-BD receptor-ionophore complexes, located in the CNS.

These results suggest that the GABA-ergic system is involved in the mechanism of peripheral regulation of uterine contractile function. The GABA-BD-receptor complexes identified in the myometrium can be used as molecular targets for potential drugs aimed at protecting the course of pregnanacy.

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NOOTROPIC ACTIVITY OF NICOTINAMIDE AND ITS STRUCTURAL ANALOGS

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KEY WORDS: nicotinamide, piracetam, nootropic activity, electron-structural analogy.

Nicotinamide is an endogenous ligand of benzodiazepine receptors and, under experimental conditions, possesses definite tranquilizing and stress-protective properties [1, 2, 4, 5, 7]. In the investigation described below nicotinamide and its structural analogs were studied as substances with nootropic activity.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino mice weighing 22-26 g. Nicotinamide in a dose of 250-1000 mg/kg and its electron-structural analogs nicomorpholine and acetylnicotinate in a dose of 10-20 mg/kg were injected intraperitoneally 30-40 min before the investigation. Acute hypobaric hypoxia was created in a chamber, and normobaric (3% oxygen and 97% nitrogen) and hemic (methemoglobin) hypoxia were created by the methods described in [3]. Antiamnesic activity was studied by the passive conditioned avoidance reflex (PCAR) method, using maximal electric shock as the factor inducing amnesia, by the method in [6]. The action of the test substances was compared with the effects of known nootropic agents: piracetam (250-1000 mg/kg), piritinol (100-200 mg/kg), and meclofenoxate (100-200 mg/kg).

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TABLE 1. Antihypoxic Activity of Nicotinamide, Nicomorpholine, and Acetylnicotinate and Comparison Preparations in Experiments on Mice (M ± m)

Experimental conditions	Hypobaric hypoxia, length of survival, min	Normobaric hypoxia			Hemic	
		percent animals surviving after exposure	length of survival, min	percent of animals surviving after exposure	length of survival, min	survival time, % of control
Control, mg/kg						
Nicotinamide	3,5±1,1		6,4±1,9		14,5±4,5	
500	8,73±3,7*	—	13,6±7,5*	—	16,2±2,6	111,4
1000	10,9±4,0*	11,9	16,7±8,6*	—	17,0±2,7	117,2
Control	2,18±1,2		7,6±1,8		14,5±4,5	
Nicomorpholine, mg/kg						
10	10,4±3,2*	22,3	20,2±6,3*	16,6	16,5±1,3	117,2
20	13,2±4,1*	48,5	25,8±5,9*	66,6	19,0±1,7	131,0
Control	2,06±0,7		7,6±1,8		13,9±1,4	
Acetylnicotinate, mg/kg						
10	9,6±3,6*	18,7	13,8±3,6*	—	18,0±3,2	129,9
20	12,1±3,9*	24,1	22,5±4,9*	16,6	18,7±4,5	135,0
Control	2,15±0,5		7,6±1,8		13,2±4,5	
Piracetam, mg/kg						
250	2,61±0,5	—	13,3±4,0*	—	12,6±2,76	95,5
500	2,78±0,7	—	13,8±5,4*	—	14,08±2,5	106,7
Control	2,4±1,0	—	—		17,05±2,3	—
Piritinol, 100 mg/kg	6,7±2,4*	—	—		19,6±2,2	113,3
Meclofenoxate, 100 mg/kg	9,6±3,5*	9,8	—		18,3±2,9	107,0

Legend. Here and in Table 2: *p < 0.05 compared with control.

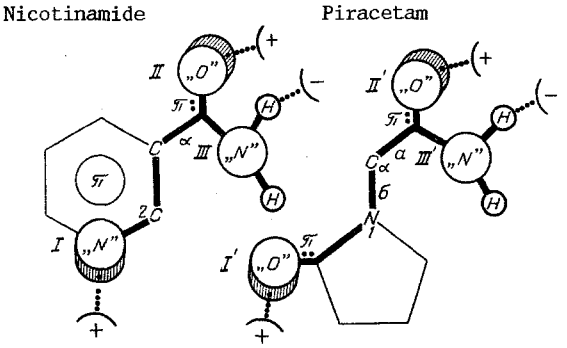

Fig. 1. Diagram (based on examination of molecular models) of the principal structural-electronic characteristics of nicotinamide and piracetam. Seeded sectors – regions of p-electrons, dots indicate possible directions of electronic interactions of molecules with receptors sites.

EXPERIMENTAL RESULTS

Experiments to study the antihypoxic activity of nicotinamide (500 mg/kg) revealed a distinct protective effect of the compound on a model of hypobaric hypoxia, as shown by lengthening of the survival of the animals by 2.5 times. With an increase in the dose of the preparation to 1000 mg/kg the antihypoxic effect was strengthened to reach 300% of the control. Nicotinamide, in the doses tested, led to lengthening of the survival rate of the animals exposed to normobaric hypoxia, and also exhibited activity in "rigorous" hemic hypoxia, increasing the survival rate (Table 1).

Nicomorpholine and acetylnicotinate were superior to nicotinamide in their antihypoxic activity, and their action was exhibited in a dose of 10-20 mg/kg. The protective effect of the new compounds was expressed both as lengthening of the average survival period of the animals in the pressure chamber (the survival rate reached 400-600%), and an increase in the number of surviving animals after an exposure of 30 min to 20-50%. Piracetam, used as the comparison drug in doses of 250-500 mg/kg gave no marked effect against pressure-chamber hypoxia. In normobaric hypoxia with oxygen deficiency in the atmosphere of the pressure chamber, nicomorpholine and acetylnicotinate protected the animals several times more successfully than piracetam and nicotinamide, increasing the survival time and also

TABLE 2. Antiamnesic Activity of Nicotinamide, Nicomorphaline, and Acetylnicotinate, and also of Comparison Preparations in Experiments on Mice

Experimental conditions	Reproduction of PCAR 24 h after training and shock		
	latent period	time spent in compartments	
	length of stay in chamber, sec:	light	dark
Control (training)	78,7 (67,0 – 90,4)	104,0 (99,2 – 108,8)	16,0 (12,3 – 19,7)
Control (training + amnesia)	16,9 (11,5 – 22,1)	45,0 (37,7 – 54,3)	75,0 (56,8 – 87,4)
Nicotinamide, 500 mg/kg	60,5 (48,1 – 72,9)*	71,0 (58,6 – 82,4)*	49,0 (24,4 – 73,6)*
Nicomorpholine, 10 mg/kg	49,5 (34,8 – 64,2)*	85,5 (61,0 – 110,0)*	34,5 (20,0 – 49,0)*
20	80,0 (67,8 – 92,2)*	108,5 (9,75 – 119,0)*	11,5 (7,9 – 15,1)*
Acetylnicotinate, mg/kg			
10	25,5 (17,0 – 34,0)*	94,0 (85,7 – 112,3)	26,0 (17,5 – 34,5)*
20	66,5 (51,8 – 81,4)*	104,0 (93,0 – 105,0)*	16,0 (11,1 – 20,9)*
Piracetam, mg/kg			
250	62,5 (50,1 – 74,9)*	64,5 (52,1 – 76,9)*	55,6 (51,3 – 65,1)
500	71,8 (57,7 – 85,9)*	82,0 (67,9 – 96,3)*	38,2 (27,0 – 49,0)*
Piritinol, mg/kg			
100	66,5 (51,8 – 81,4)*	69,5 (58,2 – 80,8)*	50,5 (38,6 – 62,4)
Meclofenoxate, 100 mg/kg	70,6 (62,6 – 79,0)*	83,0 (69,1 – 100,9)*	37,0 (30,6 – 48,4)*

the percentage of surviving animals. The tested compounds also were effective against hemic hypoxia (Table 1).

Besides their antihypoxic activity, nicotinamide, nicomorpholine, and acetylnicotinate possessed antiamnesic properties when used during the PCAR technique. These took the form of ability of the drugs to abolish the unfavorable amnesic action of electric shock on memory and to increase the length of stay of the animals in the light compartment of the experimental chamber (Table 2). Structural analogs of nicotinamide were most active under these conditions, and were effective in doses of 10-20 mg/kg.

Thus nicotinamide and its analogs possess marked antihypoxic and antiamnesic activity on various models of experimental hypoxia and amnesia, i.e., they give an effect that is similar in direction with that of the standard preparations of piracetam and meclofenoxate, evidence that nicotinamide and its analog possess nootropic properties. Furthermore, nicotinamide analogs have much stronger activity (almost an order of magnitude of doses) than the known notropic agents and nicotinamide itself.

In connection with this discovery of definite similarity between piracetam and nicotinamide with respect to several pharmacologic effects (antihypoxic, antiamnesic, anxiolytic), an attempt was made to discover structural analogy between these preparations. The problems was to examine these preparations from the point of view of their electronic, geometric, including conformational and topographic characteristics. In fact definite-electronic similarity was discovered in these compounds, in the presence and arrangement of their p- and π-electron systems and the distances between the atoms located at the polar centers of the molecules (Fig. 1). p-Electrons are bound with the positively charged receptor centers, hydrogen atoms of amide groups with centers that are negatively charged, by the formation of hydrogen bonds. The nitrogen atom (N_1) in the piracetam molecule is amide in character and it can therefore be regarded as an atom of the skeleton and fragment of the molecule simulating the carbon atom (C_2) in the nicotinamide molecule. In other words, electron-topographic complementarity of these parts of the molecule is realized. Regions II-II' and III-III' also coincide electron-topographically. The possibility of representing other conformers by rotation around the a and b bonds does not rule out the realization of identical (complementary) conformers. Amide fragments in both molecules have a flat configuration with a triangular configuration of the nitrogen atom. It is very interesting that the distance between the central electron shells of the oxygen atom of the carbonyl group and the p-electrons of the nitrogen atom of the pyridine ring, namely 5.5-6 A, agrees sufficiently well with the distance between the central electron shells of piracetam after it has acquired the appropriate conformation. During the formation of molecular-receptor complexes, the conformational requirements may change, if the energy parameters allow it.

Thus definite similarity in molecular structure can be detected by analysis of the most important structural-electron characteristics of nicotinamide and piracetam, the systems of atoms in the molecule in each of the hypothetical pharmacophores can be designated, and on that basis, the pharmacological properties of these preparations can be unified to some degree.

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ROLE OF DIHYDROPYRIDINE-SENSITIVE Ca CHANNELS IN THE PSYCHOTROPIC EFFECT OF NOOTROPIC DRUGS

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A characteristic sign of aging and age-related memory and learning disturbances is the appearance of changes in the Ca^{2+} regulating system [6, 7]. It has been shown that aging is accompanied by a decrease in the density of voltage-dependent dihydropyridine-sensitive Ca-channels (L-channels) in the cortical association areas of rats [5]. In recent years particular attention has been paid by research workers to the role of Ca channels, and of Ca^{2+} itself, in the processes of memory formation and learning [10], also in connection with the successful practical use of L-channel blockers in various pathological states [4].

In clinical practice, so-called nootropic drugs are being used for the treatment of age-related memory disturbances, and among the best known of them are piracetam and oxiracetam [9]. The mechanism of the pharmacological effect of nootropic drugs has not been completely elucidated, but there is evidence of their involvement in regulation of the cholinergic system [11-13]. In the present investigation we examined the effect of nootropic drugs on brain channels. For this purpose we studied the action of certain L-channel blockers in simple models of memory and learning, in the absence and in the presence of piracetam and oxiracetam. The results were compared with those of the study of the effect of diltiazem, a Ca^{2+}-antagonist, and of nootropic drugs on the concentration of L-channels in rat cerebral cortical membranes.

EXPERIMENTAL METHOD

Blockers of Ca-channels of L type were used: riodipine (Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR), nifedipine, diltiazem (Finland), cinnarizine (Bulgaria), verapamil (USSR), and the nootropic drugs piracetam (Latvbiofarm) and oxiracetam (Research Center for Medical Biotechnology, Ministry of Health of the USSR).

Activity of the drugs was studied on noninbred mice and male Wistar rats weighing 16-20 and 200-220 g respectively, by the method of formation of a passive conditioned avoidance reaction (PCAR), as described previously [2]. The latent period of the first departure from the starting area, and also the number of animals in the group reaching the criterion of training (staying for 5 min on the safe area 24 h after initial training) were recorded.

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