or protected with ionol was given after conditioning. Retention of BCAR also was tested after 7 days.

The results show that peak exercise, used after direct and successful conditioning of animals not receiving ionol reduced the degree of retention of the reflex by half, whereas in animals protected by the antioxidant, no such disturbance was observed (Table 2). Since the tests were carried out 7 days after exercise it is unlikely that the exercise could have disturbed recall processes. It can accordingly be postulated that the peak exercise "to the limit" disturbs fixation of the temporary connection and that ionol prevents such disturbance. This result is in agreement with the view that activation of LPO does in fact play a role in the disturbances of higher nervous activity associated with peak exercise and it opens up the prospects for prevention of such disturbances by antioxidants.

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DISTURBANCES OF THE SUPPLY OF HIGH-ENERGY COMPOUNDS TO THE BRAIN IN CHRONIC STRESS AND THEIR CORRECTION BY PSYCHOTROPIC DRUGS

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KEY WORDS: stress; psychotropic drugs; high-energy compounds; brain.

Psychoemotional stress is a basic component of unfavorable situations affecting man. Besides the widely known changes, stress also causes marked disturbances of metabolism of the brain [1, 4, 12], principally its energy metabolism [3, 5]. Correction of emotional stress includes action directed toward many links of the pathogenetic chain of development of stress reactions. A leading place among the pharmacologic agents which regulate the course of stress reactions is occupied by psychotropic drugs, specifically by tranquilizers. However, the molecular mechanisms of the protective effect of tranquilizers in stress have not been adequately studied. There are no clear ideas on the ways of realization of their pharmacologic effects.

The object of this investigation was to study the effect of tranquilizers, derivatives of different chemical groups, on the content of high-energy compounds in the brain structures of animals exposed to chronic stress.

EXPERIMENTAL METHOD

Experiments were carried out on 987 male Wistar rats weighing 220-250 g. Chronic emotional stress was produced in the form of a so-called anxiety neurosis [10] in the writer's modification, consisting of prolonged (2 h daily for 12 days) exposure of the hungry animals (deprived of food for 12 h) to the stressor, and also random alternation of a conflict situation with immobilization of the animals and electrodermal stimulation. The stress-producing action could be intensified by placing the animals in pairs in special transparent cages. Only animals with high and average levels of emotional response on preliminary testing were chosen for the experiment [11]. In this way it was possible to obtain stable changes in the biochemical parameters of the brain corresponding to the level of transition of the stage of stress from the state of compensation to one of decompensation or an excessively catabolic

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TABLE 1. Changes in Nucleotide Pool of Rat Brain Structures during Chronic Stress and Preventive Administration of Tranquilizers in Therapeutic Doses (M ± m)

Experimental conditions	ATP	ADP	AMP	Total nucleotides	Atkinson's coefficient
			Cortex		
Control	1,399±0,015	0,698±0,019	0,397±0,012	2,494±0,032	0,70±0,005
Stress	0,650±0,017[a]	0,210±0,009[a]	0,604±0,005[a]	1,464±0,024[a]	0,51±0,005[a]
Nikogamol (10 mg/kg)	1,303±0,040[b]	0,610±0,018[a,b]	0,301±0,007[a,b]	2,214±0,037[a,b]	0,73±0,005[a,b]
Litonit (10 mg/kg)	1,254±0,019[a,b]	0,708±0,011[b]	0,306±0,006[a,b]	2,268±0,031[a,b]	0,71±0,003[b]
Fenibut (10 mg/kg)	1,109±0,023[a,b]	0,701±0,009[b]	0,409±0,005[b]	2,219±0,023[a,b]	0,66±0,005[a,b]
Meprobamate (20 mg/kg)	1,002±0,030[a,b]	0,628±0,012[a,b]	0,507±0,009[a,b]	2,137±0,035[a,b]	0,61±0,007[a,b]
Chlordiazepoxide (2 mg/kg)	0,951±0,038[a,b]	0,901±0,016[a,b]	0,293±0,008[a,b]	2,145±0,037[a,b]	0,65±0,005[a,b]
Mebicar (30 mg/kg)	0,713±0,027[a]	1,011±0,014[a,b]	0,509±0,007[a,b]	2,233±0,027[a,b]	0,54±0,005[a,b]
			Limbic system		
Control	1,494±0,019	0,411±0,041	0,300±0,012	2,205±0,054	0,77±0,006
Stress	0,403±0,012[a]	0,151±0,011[a]	0,702±0,012[a]	1,256±0,019[a]	0,38±0,005[a]
Nikogamol (10 mg/kg)	1,344±0,016[a,b]	0,405±0,012[a,b]	0,300±0,006[b]	2,049±0,017[a,b]	0,75±0,004[a,b]
Litonit (10 mg/kg)	1,410±0,011[a,b]	0,619±0,017[a,b]	0,404±0,005[a,b]	2,433±0,023[a,b]	0,71±0,003[a,b]
Fenibut (10 mg/kg)	1,163±0,037[a,b]	0,611±0,008[a,b]	0,309±0,005[b]	2,083±0,036[b]	0,70±0,006[a,b]
Meprobamate (20 mg/kg)	0,909±0,031[a,b]	0,501±0,013[b]	0,606±0,009[a,b]	2,016±0,037[a,b]	0,57±0,008[a,b]
Chlordiazepoxide (2 mg/kg)	1,007±0,032[a,b]	0,748±0,015[a,b]	0,404±0,008[a,b]	2,159±0,038[b]	0,64±0,004[a,b]
Mebicar (30 mg/kg)	0,705±0,019[a,b]	0,786±0,013[a,b]	0,599±0,006[a,b]	2,135±0,021[b]	0,53±0,005[a,b]
			Medulla		
Control	1,600±0,019	0,597±0,022	0,492±0,012	2,689±0,037	0,71±0,005
Stress	1,202±0,021[a]	0,402±0,012[a]	0,302±0,006[a]	1,906±0,019[a]	0,74±0,005
Nikogamol (10 mg/kg)	1,318±0,041[a,b]	0,704±0,014[a,b]	0,253±0,005[a,b]	2,275±0,049[a,b]	0,73±0,004[a]
Litonit (10 mg/kg)	1,357±0,016[a,b]	0,907±0,019[a,b]	0,221±0,006[a,b]	2,485±0,024[a,b]	0,73±0,003[a]
Fenibut (10 mg/kg)	1,405±0,036[a,b]	0,799±0,016[a,b]	0,200±0,007[a,b]	2,404±0,045[a,b]	0,75±0,003[a]
Meprobamate (20 mg/kg)	1,310±0,039[a,b]	0,803±0,009[a,b]	0,266±0,006[a,b]	2,379±0,044[a,b]	0,72±0,006[b]
Chlordiazepoxide (2 mg/kg)	1,202±0,028[a]	0,703±0,011[a,b]	0,495±0,010[a,b]	2,400±0,037[a,b]	0,65±0,004[a,b]
Mebicar (30 mg/kg)	1,251±0,026[a]	0,596±0,015[a,b]	0,202±0,007[a,b]	2,149±0,030[a,b]	0,74±0,005[a]

Legend. a) $P < 0.05$ compared with control, b) $P < 0.05$ compared with stress.

situation [6]. Widely known tranquilizers — chlordiazepoxide and meprobamate, derivatives of natural human metabolites — fenibut (β-phenyl-γ-aminobutyric acid) and mebicar [2,4,6,8-tetramethyl-2,4,6,8-tetra-azobicyclo-(3,3,0)-octadione-3,7], and also derivatives of GABA and nicotinic acid obtained in the writer's laboratory (nikogamol and litonit) were used as protectors. Therapeutic doses of the tranquilizers were chosen by calculating ED_{50} in the following tests: activity in a conflict situation, effect on external inhibition, nonreinforcement of actions and a new situation (orienting reflex). The substances were injected intraperitoneally and physiological saline was given to the control animals. The concentrations of high-energy compounds were determined in homogenates of the cortex, limbic system (hippocampus, hypothalamus, and amygdala), and in the medulla by an enzymic method [9], using "Test-Combination" kits of reagents (West Germany). The brain was isolated in the cold and subsequently frozen in liquid nitrogen. Concentrations of high-energy compounds were expressed in micromoles/g tissue. The adenylate charge was expressed in the form of the coefficient [8]. The experimental results were subjected to statistical analysis on the Minsk-22m computer.

EXPERIMENTAL RESULTS

Investigation of the biochemical parameters of the brain at different stages of development of stress, and also the indirect control monitoring ulcer and erosion formation in the stomach, the glycogen concentration, morphometry of the adrenals, and the mitochondrial morphology showed that a 12-day program of exposure to stress by this method induces definite changes and, most important of all, consistently repeated changes in the concentration of high-energy compounds — among the principal biological substrates for oxidative processes and biosynthesis [7]. Stress led to sharp changes in the concentration of adenine nucleotides (AN) in the brain. The ATP concentration in the cortex was reduced by more than half and in the limbic system by almost two-thirds. Despite the decrease in the ATP concentration in the medulla (by 25%), changes here were less marked than in other structures studied. Parallel with ATP, the ADP concentration also fell: by 71% in the cortex and limbic system and by 50% in the medulla. The ATP concentration in the cortex and limbic system rose, whereas in the medulla it fell. The total concentration of high-energy compounds in all structures

fell mainly on account of ATP and ADP. Because of the considerable decrease in the ATP and ADP concentrations, the degree of saturation of AN by high-energy phosphate fell chiefly in in the cortex and limbic system, whereas in the medulla this parameter was unchanged (Table 1). It can be concluded from analysis of these data that stress led to a sharp decrease in the AN pool in the cortex and limbic system. This was evidently connected with changes in the functional state of the neurons under stress conditions. The medulla (brain-stem formations) was less susceptible to the action of stress, and a decrease in the AN concentration in it was less marked than in the cortex and limbic system. This "inertia" of the medulla toward stress can be explained by its phylogenetically established function, devoted to self-regulation of the life-support systems [2].

Administration of a preventive course of the psychotropic drugs against the background of chronic stress not only reduced ulcer formation, restored the normal morphology of the adrenals and mitochondria, but also considerably restored the normal concentration of high-energy compounds in the brain (Table 1). The preparations studied increased the ATP concentration in all brain structures, when considerably reduced by stress. The increase in ATP was observed mainly in the limbic system (up to 300% or more), where stress had reduced the concentration of this high-energy compound by 71% (0.403 ± 0.012 μmole/g tissue compared with 1.494 ± 0.019 μmole/g in the control), next — in the cortex (up to 200%), where its concentration was 0.650 ± 0.017 and 1.399 ± 0.015 μmole/g tissue respectively. In the medulla stress caused no significant change in the ATP concentation, and after administration of tranquilizers only a tendency was observed for its level to rise here. The ADP concentration also increased in all the structures studied, but by a greater degree than that of ATP (in the cortex and limbic system the increase was from 200 to 500% respectively). Whereas the ATP concentration increased more in the limbic system, the ADP level rose in the cortex and limbic system almost proportionally. Characteristically the ADP concentration in the medulla (unlike ATP) rose significantly and amounted to 200% or more. It must also be noted that under the influence of the drugs the ADP concentration in the medulla rose by a much greater degree than in the control.

Under the influence of the drugs tested the AMP concentration fell about equally in all structures. The exception was chlordiazepoxide, which increased the AMP concentration in the medulla. Stress increased the AMP concentration considerably in all structures. All the psychotropic drugs increased the nucleotide pool, and the total AN did not differ significantly in the brain structures before and after administration of the drugs. Meanwhile the increase in the total AN after the use of the different drugs took place on account of different high-energy compounds. For instance, the increase in total AN after administration of nikogamol, litonit, and fenibut took place chiefly on account of ATP and led to normalization of the adenylate charge (Atkinson's coefficient was restored). Under the influence of mebicar, meprobamate, and chlordiazepoxide the increase in total AN took place mainly on account of ADP and AMP and it did not restore the normal adenylate charge.

It can be concluded from the facts described above that all the preparations studied have a protective action in stress and restore the normal concentrations of high-energy compounds in the brain. Drugs based on natural metabolites (nikogamol, litonit, and fenibut) have the strongest effect. Mebicar is close to them in the direction of its action, but its effect is weaker. Meprobamate and chlordiazepoxide, while restoring normal behavioral responses when disturbed by stress, are less effective in restoring the normal concentration of high-energy compounds in the brain.

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