the number of rotations vis-a-vis the control was the same as that induced by 5-MeODMT. This is probably connected with a partial agonism of buspirone to the 5-$HT_{1A}$ receptors, because buspirone is known to diminish the serotoninergic syndrome caused by 8-oxy-2-(di-n-propylamino)-tetraline (a selective agonist of 5-$HT_{1A}$ receptors) [8]. A blocker of the $D_2$ autoreceptors, buspirone has a modulatory effect on DA synthesis and promotes local release of DA from the dendrites of SN, by activation of the supersensitive somatodendritic 5-$HT_{1A}$ postsynaptic receptors. Evidently, inhibition of hyperpolarization during the transmission of impulses to SN is hindered by buspirone blocking the somatodendritic $D_2$ autoreceptors, DA release being induced in the ipsilateral striatum. A buspirone-induced DA release can be observed in the corpus striatum itself, this compensating on the whole for the specific disturbances of 5-HT neurotransmission. Such a combined action of buspirone on the DA autoreceptors and 5-$HT_{1A}$ receptors in rats with unilateral lesions of DNR and MNR is achieved not only in the mesostriatal, but also in the mesolimbic structures, where the anxiolytic effect of the preparation is mainly realized.

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# Effects of N-Acetylaspartic Acid on the Brain after Frontal Lobectomy in Rats: Antiamnestic Effect and Influence on Monoamine Content

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N-acetylaspartic acid (AcAA) is a neurospecific substance found in diverse regions of the CNS, its concentration in the brain tissue being inferior only to that of glutamic acid, along with which it is produced by enzymolysis of the N-acetylaspartylglutamate dipeptide. The latter is considered to be a possible excitatory neurotransmitter [5, 8]. It has been established that AcAA is able to accelerate spatial learning in a water maze, to improve performance of the conditioned passive avoidance response (CPAR) disturbed by transcorneal electroshock or by the injection of the NMDA-receptor antagonist MK-801, and also to prevent the natural extinction of the habit [3].

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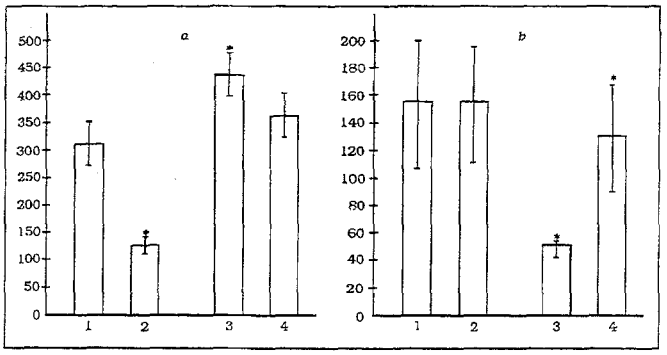


**Fig. 1.** Effect of AcAA on horizontal activity "in the open field" (*a*) and latent period of CPAR (*b*) on the 9th day after frontal lobectomy. *a*) number of squares crossed. within 300 sec, *b*) latent period of CPAR (sec, $M \pm m$). Abscissa: groups of animals. Reliability of differences ($p<0.05$) with respect to group 1 is shown by an asterisk, and with respect to group 3, by a circle (8–12 rats in each group).

The mechanism of AcAA influence on the processes of learning and memory remain unstudied; however, data are available indicating the participation of AcAA in brain metabolism, including monoamine exchange [6, 7, 11-13]. It has been shown previously that amnesia caused by extirpation of the frontal cortex in rats is accompanied by disturbances of conditioned response behavior and also by changes in the neurochemical systems of the brain [2, 10].

The aim of the present investigation was to study the influence of AcAA on the performance of CPAR and on the content of monoamines: noradrenalin (NA), as well as dopamine (DA) and serotonin (5-HT) and their metabolites dioxyphenylacetic (DOPAA) and 5-hydroxyindoleacetic (5-HIAA) acids, in brain structures during the period of disturbed integrative CNS activity following frontal lobectomy in rats.

## MATERIALS AND METHODS

The experiments were carried out on 43 noninbred albino male rats weighing 200-250 g. Motor activity of the animals tested "in the open field" was evaluated with the aid of a RODEO device recording 4 parameters: horizontal activity (number of squares crossed), vertical activity (standing postures), and exploratory activity (study of the upper and lower holes in the box). After that, CPAR was elaborated and the latent period (LP) of the first movement from the lit into the dark compartment of the box was determined [1]. In the trained animals narcotized with nembutal (40 mg/kg, intraperitoneally) a bilateral extirpation of the frontal zones of the cortex was performed according to a previously described method [10]. Animals of the control group underwent a sham operation of skull trephination without any injury to the cerebral cortex. AcAA was administered daily beginning from the day after the operation once a day in a dose of 50 mg/kg intraperitoneally, on 9 consecutive days. The animals were divided into groups:

**TABLE 1.** Effect of N–acetylaspartic Acid (AcAA) on Content of Monoamines and Their Metabolites in Brain Structures on Day 9 after Frontal Lobectomy (FLE) and in Animals Undergoing a Sham Operation (SO)

| Group of animals | Content of transmitters and their metabolites ($m \pm M$), ng/mg tissue | | | | |
|---|---|---|---|---|---|
| | NA | DA | DOPAA | 5-HT | 5-HIAA |
| | | | Parietal cortex | | |
| 1. SO+NaCl | 0.43±0.30 | 0.032±0.012 | – | 0.23±0.01 | 0.22±0.02 |
| 2. SO+AcAA | 0.32±0.03* | 0.015±0.001* | – | 0.22±0.01 | 0.23±0.02 |
| 3. FLE+NaCl | 0.13±0.01* | 0.012±0.003* | – | 0.12±0.01 | 0.15±0.02* |
| 4. FLE+AcAA | 0.17±0.02 | 0.012±0.002 | – | 0.10±0.01 | 0.10±0.02° |
| | | | Hypothalamus | | |
| 1. SO+NaCl | 1.62±0.10 | 0.282±0.020 | 0.10±0.01 | 0.65±0.04 | 0.83±0.03 |
| 2. SO+AcAA | 1.96±0.11* | 0.343±0.032 | 0.11±0.01 | 0.76±0.03* | 1.01±0.02* |
| 3. FLE+NaCl | 1.84±0.09 | 0.311±0.024 | 0.10±0.03 | 0.79±0.03* | 0.89±0.03* |
| 4. FLE+AcAA | 2.11±0.10° | 0.348±0.043 | 0.10±0.01 | 0.85±0.04 | 0.97±0.04 |
| | | | Corpus striatum | | |
| 1. SO+NaCl | 0.38±0.05 | 8.129±0.164 | 1.46±0.07 | 0.45±0.03 | 1.04±0.07 |
| 2. SO+AcAA | 0.37±0.04 | 7.520±0.379 | 1.40±0.06 | 0.51±0.03 | 1.20±0.10 |
| 3. FLE+NaCl | 0.37±0.03 | 6.945±0.479 | 1.09±0.08* | 0.67±0.03* | 1.51±0.06* |
| 4. FLE+AcAA | 0.40±0.06 | 6.356±0.497 | 1.30±0.09 | 0.58±0.03° | 1.57±0.07 |
| | | | Adjacent nucleus | | |
| 1. SO+NaCl | 0.53±0.07 | 3.290±0.226 | 0.61±0.07 | 0.38±0.05 | 0.47±0.03 |
| 2. SO+AcAA | 0.64±0.05 | 3.013±0.210 | 0.61±0.05 | 0.43±0.02 | 0.53±0.01* |
| 3. FLE+NaCl | 0.77±0.07* | 2.504±0.210* | 0.50±0.04 | 0.41±0.03 | 0.56±0.02* |
| 4. FLE+AcAA | 0.59±0.09 | 2.544±0.261 | 0.48±0.05 | 0.43±0.04 | 0.54±0.05 |

**Note:** Reliability of differences ($p<0.05$) with respect to group 1 is shown by an asterisk, and with respect to group 3 by a circle (each group comprises 8–12 rats).

group 1 - animals undergoing the sham operation + 0.9% NaCl (control for groups 2 and 3); group 2 - sham operation + AcAA; group 3 - frontal lobectomy + 0.9% NaCl (control for group 4); group 4 - frontal lobectomy + AcAA. Motor activity and CPAR performance were evaluated on the 9th day after the operation, when the changes of monoamine metabolism are most pronounced [2]. The determination of the content of monoamines and their metabolites was performed by the method of HPLC/ED [4].

## RESULTS

The results of our investigation show that frontal lobectomy is accompanied by an increase of motor activity in animals tested "in the open field", in particular, a 41% increase of horizontal movements (see Fig. 1, *a*). AcAA induced a decrease of this parameter by 17% compared to that found in the control group. In animals undergoing a sham operation AcAA also caused a decrease of motor activity by 57% with respect to the control group.

Frontal lobectomy is attended by significant disturbances of memory trace preservation, manifested in a decrease of the LP duration during CPAR performance (see Fig. 1, *b*). No marked changes in the LP of CPAR were observed in sham-operated rats vis-a-vis the trained animals undergoing no operation, these results being in agreement with previous investigations [10]. As the data presented show, the LP of CPAR in the lobectomized rats receiving AcAA increased 139%, thereby demonstrating a significant improvement of memory trace preservation.

The results of the biochemical investigations are presented in Table 1. AcAA caused a 26% decrease of NA content in the parietal cortex in animals undergoing the sham operation and a 53% decrease of DA content. In the hypothalamus of these animals AcAA induced an increase of 5-HT, 5-HIAA, and NA by 17, 22, and 21%, respectively; in the adjacent nucleus the concentration of 5-HIAA rose 12% in comparison with the control group. In brain structures of the rats subjected to frontal lobectomy important changes in monoamine metablism are revealed vis-a-vis those found in animals undergoing a sham operation. The monoamine content in the parietal cortex was significantly lower than the control values: of 5-HT by 50%, of 5-HIAA by 32%, of DA by 63%, and of NA by 71%. A significant increase of the 5-HT content (by 53%) and of the 5-HIAA content (by 44%) was noted in the corpus striatum of lobectomized rats; the rise of the 5-HT and 5-HIAA content in the hypothalamus and the adjacent nucleus was less marked and did not exceed 21%. At the same time, reduced parameters of DA metabolism were found in the adjacent nucleus and in the corpus striatum of lobectomized rats. The observed decrease in the 5-HT and 5-HIAA content in the cerebral cortex and the increase of their concentration in the subcortical structures accompanying the drop in the 5-HT content in the parietal cortex may attest to increased 5-HT utilization in the brain of the rats subjected to frontal lobectomy. The serotonin exchange coefficient (EC), expressed by the equation: (c)5-HIAA / (c)5-HT, where (c) is the monoamine or metabolite content, increased from $0.929\pm0.052$ in animals undergoing a sham operation to $1.263\pm0.072$ in lobectomized rats ($p<0.05$). AcAA injection to animals with frontal lobectomy was accompanied by a further decrease of the 5-HIAA content (by 34%) in the parietal cortex. At the same time the EC of serotonin in animals receiving AcAA ($1.017\pm0.119$) proved to be reliably lower than the corresponding values in operated untreated rats ($1.263\pm0.072$), demonstrating a serotoninergic process normalization in the parietal cortex under the influence of AcAA. AcAA induced a decrease of 5-HT concentration in the corpus striatum by 15% with respect to the control values (lobectomy), leading to a certain normalization of the 5-HT content. The EC of 5-HT increased reliably from $2.292\pm0.122$ in the control to $2.738\pm0.155$ in operated and treated animals. No regular changes of monoamine metabolism in the hypothalamus and the adjacent nucleus could be determined in rats of this group. The results are in agreement with published data [11] showing that the changes of 5-HT and isogenic AcAA induced by diverse pharmacological preparations occur in a single direction.

The results thus suggest that one of the ways in which the effect of AcAA on CNS integrative functions is implemented is by modulation of the functional activity of the monoaminergic systems in the brain. The AcAA-induced normalization of the exchange rate of serotonin in the brain of rats after frontal lobectomy is obviously of great importance.

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# The Properties of Glucocorticoid-Sensitive Alkaline Proteinases of Rat Target Organs

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**Key Words:** *dexamethasone; alkaline proteinases; thymus; liver*

When used in clinical treatment, pharmacological agents with glucocorticoid-like activity cause such complications as immunodepression, myatrophy, and connective tissue degeneration [3,4,7]. These side effects result from aggravated protein degradation. However, the mechanisms whereby glucocorticoids and their synthetic analogs exert their catabolic or, in the liver cells, anabolic effects are still unknown [1].

The glucocorticoid-sensitive cells have been recently shown to possess alkaline proteinases (AP), proteolytic enzymes with the activity optimum within the alkaline range of pH values [8,10-12]. Glucocorticoid administration *in vivo* enhances AP activity in the thymus [2] and skeletal muscles [5,6].

However, the properties of glucocorticoid-sensitive AP are poorly understood. The peculiarities of glucocorticoid-activated AP in the skeletal muscles have been partially described [9,13].

In the present study the preliminary characteristics of rat thymus and liver AP induced by dexamethasone-21-Na-phosphate were obtained.

## MATERIALS AND METHODS

Unbred albino male rats were used for the experiments. The rats received 2 mg/kg dexamethasone in 0.5 ml intraperitoneal injection 24 h before decapitation. Decapitation was carried out under light ether narcosis. The thymus and liver were removed and placed on ice. AP activity in the tissue homogenates was determined by measuring the rate of azocasein hydrolysis [2].

5,5'-dithio-bis(2-nitrobenzoic acid) (DTNB), L-5-amino-1-p-toluenesulfonyl amidopentylchloromethaneketone (TACK), L-1-(p-toluenesulfonyl)amido-2-phenylethanechloromethaneketone (TPCK), and phenylmethanesulfonyl fluoride (PMSF) were dis-

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