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ROLE OF MONOAMINES IN RECOVERY OF CONDITIONED REFLEX ACTIVITY AFTER FRONTAL LOBECTOMY IN RATS

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The role of the monoaminergic system of the brain in integrative processes in the CNS — behavior, learning, memory — is widely known [4, 5, 7, 8]. At the same time, it has been shown that most diseases of the CNS are based on a disturbance of neurochemical processes in the brain, in conjunction with other mechanisms [1, 2, 12-15]. An essential condition for the successful compensation of these disturbances by drugs is knowledge of the mechanisms of the pathological changes in neurotransmitter systems.

The writers showed previously [3, 9] the injury to the frontal cortex of the rat brain is accompanied by changes in serotonin (5-HT) metabolism in the cerebral cortex and deep brain structures.

It was decided to study the character of changes in monoamine — 5-HT, noradrenalin (NA), dopamine (DA) — levels in the development of compensation recovery after bilateral injury to the frontal cortex.

EXPERIMENTAL METHOD

Chronic experiments were carried out on 23 noninbred male albino rats weighing 180-200 g. The functional state of integrative activity of the brain was assumed on the basis of conditioned reflex parameters. Conditioned motor feeding reflexes were formed in the animals in a specially equipped chamber, with two-way reinforcement in response to photic and acoustic stimuli. Conditioned relfexes were considered to be formed if 80-100% of correct responses were obtained on each of 3 successive days.

At the end of conditioning the animals were divided into two groups: 1) rats undergoing a mock operation; 2) animals undergoing frontal lobectomy. The state of conditioned reflex activity was tested daily after the operation. On the 9th day after lobectomy the rats were decapitated and the brain removed for biochemical investigation.

Concentrations of NA, DA, 5-HT, dihydroxyphenylacetic acid (DHPAA), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA) were determined in the cerebral cortex, hypothalamus, corpus straitum, hippocampus, and brain regions including the nuclei raphe and locus coeruleus [6, 10]. The results were subjected to statistical analysis by Student's test. Monoamine levels in structures of the rat brain were determined by high-performance liquid chromatography with electrochemical detection [11].

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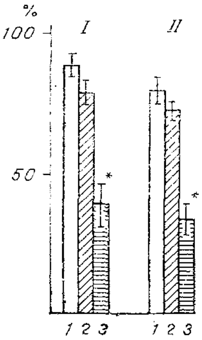

Fig. 1. Effect of frontal lobectomy in rats on conditioned motor reflex with two-way reinforcement: I) level of performance of reflex to photic stimulus; II) the same, the acoustic stimulus. 1) Before operation; 2) on 9th day, animals undergoing mock operation; 3) on 9th day after lobectomy. *P ≤ 0.001.

Brain tissue was homogenized in 0.1M $HClO_4$ containing 100 mg/ml of dihydroxybenzylamine (DHBA). The samples were then centrifuged at 15,000g for 10 min. The supernatant was filtered by centrifugation through cellulose filters with pore diameter of 0.2 μ; 20 μl of filtrate was applied to the column. Catecholamines and indoleamines were separated on an LC-304 chromatograph (BAS, USA), equipped with a 7125 Reodyne injector (USA) with 20-μl loop for introducing the samples. Amines were separated by means of a 4.6 × 250 mm octadecylsilane biophase column, with PS = 18.5 μ, protected by a 4.6 × 30 mm precolumn, with PS = 18.10 μ. The column was kept at a constant temperature of 45°C. A twin LC-4B amperometric detector with LC-17D cells and with two glass-carbon TL-5 electrodes was used as the detector. Potentials applied to the working electrodes were: +650 and +650 mV against an RE-1 Ag/AgCl reference electrode. The flow rate was 1 ml/min. Separation was carried out in 0.02 M citrate-phosphate buffer, pH 3.6, containing 0.3 mM sodium octylsulfite and 4% acetonitrile.

EXPERIMENTAL RESULTS

Extirpation of the frontal cortex of the rats led, within a few days after the operation, to a marked decrease in the number of correct conditioned-reflex responses to both photic and acoustic stimulation. The animals' general behavior also was changed: the rats exhibited motor excitation, gave intertrial responses, and performed pendulum movements from one feeding bowl to another. The time course of recovery of conditioned-reflex activity after injury to the frontal cortex, described by the writers previously [3], is evidence of a sufficiently high degree of recovery of the conditioned reflexes by the 9th day. The number of correct responses of animals of the experimental group by this time averaged 39% to the photic and 33% to the acoustic stimulus. The corresponding proportions for control animals undergoing the mock operation were 78 and 72% (Fig. 1).

Besides assessing the functional state of the CNS on the basis of parameters of conditioned-reflex activity, biochemical analysis was undertaken to determine monoamine levels in various brain structures at the same time after frontal lobectomy. Data on concentrations of the neurotransmitters tested and their metabolites in the brain structures of control animals undergoing the mock operation are given in Table 1.

The analysis showed a marked decrease in concentrations of 5-HT, 5-HIAA, and NA in the cerebral cortex and of DA in the corpus striatum on the 9th day after lobectomy. The 5-HT level in the parietal and occipital cortex fell by 35 and 44%, respectively, compared with the control, taken as 100%.

TABLE 1. Monoamine Concentrations in Brain Structures of Control Rats After Mock Operation (M ± m)

Monoamines and their metabolites	Brain structure					
	parietal cortex	occipital cortex	corpus striatum	nuclei raphe	locus coeruleus	hypothalamus
NA	3,66±0,34	4,25±0,75	4,45±0,50	19,01±1,66	49,39±2,81	11,95±0,83
DA	—	—	54,1±1,80	1,92±0,18	4,54±0,30	1,94±0,35
DHPAA	—	—	7,30±0,47	—	6,92±0,39	0,85±0,11
HVA	—	—	4,81±1,17	—	—	—
5-HT	1,23±0,02	1,01±0,07	2,54±1,00	9,06±0,81	23,48±1,80	2,30±0,22
3-HIAA	1,20±0,08	1,12±0,07	4,14±0,90	15,27±1,11	34,72±2,59	4,12±0,54

Legend. Mean results of five or six experiments given (in pmoles/mg wet weight of tissue).

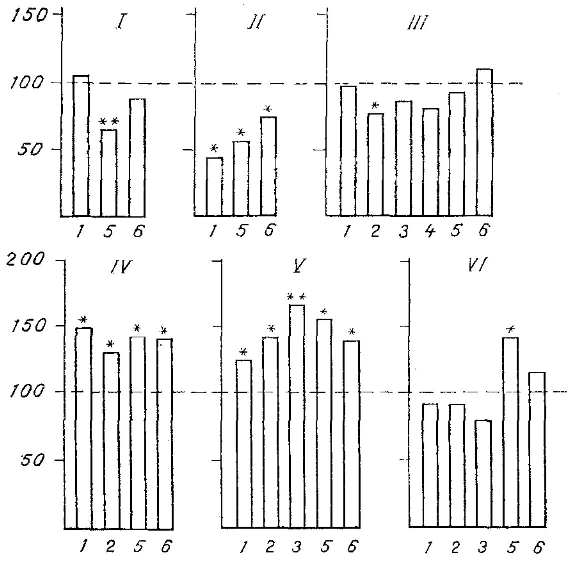

Fig. 2. Concentrations of monoamines and their metabolites in brain structures on 9th day after lobectomy in rats. 1) NA; 2) DA; 3) DHPAA; 4) HVA; 5) 5-HT; 6) 5-HIAA. I) Parietal cortex; II) occipital cortex; III) corpus straitum; IV) nuclei raphe; V) locus coeruleus; VI) hypothalamus. Mean results of five or six experiments shown. Values expressed in percentages of control values, taken as 100% (Table 1). *$P < 0.05$, **$P < 0.001$ compared with control.

Changes in 5-HIAA and NA concentrations were more marked in the occipital cortex. The DA level in the corpus striatum was 24% lower than in the control. In brain regions including the nuclei raphe and locus coeruleus a considerable increase in concentrations of 5-HT, 5-HIAA, NA, DA, and DHPAA was observed compared with the control, whereas in the hypothalamus the 5-HT level was raised by 33% (Fig. 2). Changes in concentrations of these neurotransmitters were not observed in the hippocampus.

During the development of compensatory and repair processes in the CNS after lobectomy, adaptation of 5-HT, NA, and DA metabolism thus took place, as shown by a fall in their levels in brain structures containing terminals of monoaminergic neurons. At the same time, concentrations of the monoamines and their metabolites increased in the deep brain structures. These changes reflect compensatory mechanisms of the responses of the brain after its injury. Pharmacological intervention directed toward monoamine metabolism with the aim of optimizing monoamine levels in the brain may be one component of the treatment program for neurological and neurosurgical patients.

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