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GENESIS OF AMNESIAS INDUCED BY ELECTROCONVULSIVE SHOCK

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UDC 616.89-008.464-02:615.869

The effect of a series of repeated electric shocks (ES) on preservation of conditioned reflexes and on the concentration of free amino acids (AA) in the rat brain was studied. Under the influence of repeated ES, the first of which was applied 24 h after irradiation, the rats developed amnesia. The excitatory AA concentration in the brain was unchanged, but the concentrations of inhibitory AA and also of phenylalanine and tyrosine fell sharply. The AA concentration in the blood plasma rose. It is suggested that the onset of amnesia was due to a change in the balance between excitatory and inhibitory AA in favor of the former. A definite role in the genesis of these disturbances may be played by changes in the functional state of the blood-brain barrier.

KEY WORDS: amnesia; free amino acids in the brain; blood-brain barrier.

Despite numerous investigations into the nature of retrograde amnesia induced by electroconvulsive shock (ECS) the genesis of this phenomenon is still largely unexplained [6]. Nevertheless, the elucidation of the mechanism of development of amnesias induced by ECS is of great importance not only for the solution of many fundamental problems in the neurobiology of memory, but also for the further theoretical study and effective use of electroconvulsive therapy in clinical practice. One effective way of studying the mechanisms of amnesias induced by ECS is the investigation of metabolic changes in the brain. In this respect the investigation of the content of free amino acids (AA) is of considerable interest, for besides their participation in protein metabolism, AA perform the role of neuromediators and participate in the synthesis of the "classical" neuromediators. One of us (L.G.P.) showed previously that a single ECS, causing retrograde amnesia, leads to marked changes in the absolute content and relative proportions of AA, detectable both at once and, in particular, 24 h after ECS [3]. It was suggested that the most likely cause of the retrograde amnesia is a disturbance of engram recall.

The object of the present investigation was to study the effect of, not one, but repeated ECS on preservation of the temporary connections and on the AA content in the brain. To test the hypothesis that ECS affects predominantly the operation of recall, the first of a

Laboratory of Neurochemical Mechanisms of the Conditioned Reflex, Institute of Higher Nervous Activity and Neurophysiology, Academy of Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR A. M. Chernukh.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 87, No. 4, pp. 295-297, April, 1979. Original article submitted May 3, 1978.

 0007-4888/79/8704-0290$07.50

TABLE 1. Effect of a Series of ECS on Preservation of CPAR (M ± m)

Group of animals	Time of stay in "safe" compartment of apparatus	
	in original experiment	during testing of CPAR
Control (n = 15)	6,2±0,94	210,86
Experimental (n = 21)	4,65±0,86	23,71*

* $P<0,05$.

series of daily ECS was applied 24 h after learning, i.e., after completion of the consolidation process. In view of data showing the effect of ECS on the state of the blood-brain barrier (BBB) [1, 4, 11] and the possible role of these disturbances in the changes in the brain AA content, AA concentrations were investigated not only in the brain, but also in the blood.

EXPERIMENTAL METHOD

Experiments were carried out on albino rats weighing 180-200 g. In one test a conditioned passive avoidance reflex (CPAR) was produced in the animals by the method described in [9]. The first ECS was given to the experimental rats 24 h later, and ECS were applied subsequently daily for 15 days. The ECS was produced by passing a current through electrodes applied to the parietal regions of the skull. After formation of the CPAR, mock ECS were given to the control animals by the same scheme as to the experimental rats. Preservation of the CPAR was tested in the control and experimental animals 24 h after the last ECS, after which the animals were decapitated and their brain extracted for biochemical investigation. The brain was homogenized manually in 4.4% sulfosalicylic acid solution. The concentration of free AA in the brain and blood was studied [8] with the KLA-3B amino acid analyzer (Hitachi).

EXPERIMENTAL RESULTS

Testing preservation of the CPAR 24 h after the 15th ECS revealed distinct amnesia although this reflex was sufficiently well preserved in the control animals (Table 1).

Data on the AA concentration in the brain of the control and experimental animals are given in Table 2.

As Table 2 shows, under the influence of repeated ECS the concentrations of histidine, proline, and cystine in the brain fell sharply (below the sensitivity of the instruments); the concentrations of arginine, threonine, glycine, tyrosine, and phenylalanine also fell considerably; the concentrations of serine, alanine, and isoleucine increased and those of

TABLE 2. Effect of Repeated ECS on Concentration of Amino Acids in Brain (in μmoles/g wet weight) and Blood (in μmoles/ml plasma) (M ± m)

Amino acid	Control			Experiment		
	brain	blood	brain/blood ratio	brain	blood	brain/blood ratio
Lysine	0,09050±0,0013	0,2025±0,024	0,44	0,1316+0,030	0,3412±0,044	0,38
Histidine	0,0209±0,0032	0,0418±0,007	0,50	Not determined	0,0675±0,019	0
Arginine	0,0487±0,0039	0,0706±0,012	0,69	0,0251±0,005*	0,1596±0,008*	0,15
Aspartic Acid	1,5764±0,0387	0,0307±0,008	51,34	1,7090±0,270	0,0908±0,011*	18,82
Threonine	0,7960±0,1390	0,3062±0,021	2,59	0,1320±0,027*	1,3178±0,039*	0,10
Serine	0,2694±0,030	0,3571±0,011	0,75	0,4386±0,060*	0,5729±0,026*	0,76
Glutamic Acid	6,4302±0,3118	0,0877±0,004	73,32	6,4059±0,700	0,1951±0,009*	32,83
Proline	0,0914±0,0048	0,1900±0,012	0,48	Not determined	0,3836±0,017*	0
Alanine	0,3425±0,049	0,2606±0,014	1,31	0,5256±0,025*	0,9814±0,056*	0,53
Glycine	0,5935±0,0316	0,1870±0,006	3,17	0,2081±0,005*	0,7165±0,019*	0,29
Cystine	0,0286±0,0062	0,0311±0,007	0,91	Not determined	0,0568±0,009	0
Valine	0,4113±0,0054	0,0478±0,009	8,60	0,0377±0,008	0,1744±0,021*	0,21
Methionine	0,0182±0,0029	0,0265±0,004	0,68	0,0118±0,004	0,0476±0,008*	0,24
Isoleucine	0,0152±0,0013	0,0312±0,002	0,48	0,0223±0,002*	0,0810±0,011*	0,27
Leucine	0,0283±0,0027	0,0451±0,003	0,62	0,0299±0,002	0,1585±0,084*	0,18
Tyrosine	0,0437±0,0079	0,0813±0,010	0,53	0,0255±0,002*	0,0790±0,006	0,32
Phenylalanine	0,0315±0,004	0,0338±0,008	0,93	0,0236±0,002*	0,0539±0,008*	0,43

* $P<0,05$.

aspartic and glutamic acids showed no significant change. Changes in the AA concentration in the brain were accompanied by an increase in their blood levels, except for tyrosine, the blood concentration of which was unchanged under the influence of repeated ECS. When these results are assessed it must be emphasized above all that, while the level of exciting AA (glutamate and aspartate) in the brain of the experimental animals remained unchanged, the concentrations of inhibitory AA (glycine and proline) fell (to zero). As a result of this the balance between excitatory and inhibitory AA shifted sharply toward predominance of the former (in the control the ratio of glutamate + aspartate to glycine + proline was 11.69, compared with 38.99 in the experimental series). It must also be remembered that, according to existing evidence [10, 12], proline is a natural physiological antagonist of glutamate. By blocking glutamate receptors, proline "moderates" the excitatory effects of glutamate. So far as glycine is concerned, it is regarded as an inhibitory neuromediator at the brain-stem level [5], but there is some evidence that glycine also has an inhibitory action on cortical neurons [5]. The decrease in the concentrations of phenylalanine and tyrosine in the brain of the experimental animals also deserves attention, for this must involve a decrease in the catecholamine concentration, as was in fact observed [2]. A decrease in the brain noradrenalin concentration is known [7] to be accompanied by a marked deficiency of inhibition. One result of these changes in the concentrations of free AA may evidently be a sharp rise in the excitability of the higher levels of the CNS and a profound efficiency of inhibition in the experimental animals. Under these conditions disturbance of preservation of CPAR is probably the result of disinhibition of the CPAR, which is an inhibitory conditioned reflex.

An important role in the mechanism of the changes in the AA concentration in the brain of the experimental animals was evidently played by disturbances of function of the BBB caused by repeated ECS. Analysis of the ratios between the AA concentration in the brain and the blood shows that under the influence of repeated ECS the permeability of the BBB is reduced for virtually all AA. Under these circumstances the BBB completely loses its permeability to histidine and cystine and remains virtually impermeable to proline (which for practical purposes under normal conditions does not pass from the blood into the brain). Considering that penetration of AA from the blood into the brain reflects the regulatory function of the BBB, disturbances of this aspect of BBB activity may be supposed to play a definite role in the origin of the retrograde amnesia caused by ECS.

The authors are grateful to Professor K. I. Pogodaev and Dr. Biol. Sci. N. F. Turova for providing facilities for the investigations.

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