krein nor factor XIIa nor plasmin [1] can activate factor X and, consequently, in such situations the possibility that activation of prothrombin into thrombin by these enzymes takes place indirectly, through its physiological activator factor Xa, must be ruled out.

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ROLE OF THE MESENCEPHALIC RETICULAR FORMATION IN HORMONE PRODUCTION DURING CHRONIC EMOTIONAL STRESS

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UDC 612.43/.45.018-06:612.826.5-06:613.863

KEY WORDS: stress; bioelectrical activity; hormones; reticular formation.

Investigations of the neurohormonal mechanisms of chronic emotional stress revealed correlation between the functional state of the CNS and hormonal secretion [1, 2]. In continuing the search for neuronal correlates of hormonal secretion, the writers directed their attention to the mesencephalic reticular formation (MRF) which, together with hypothalamic formations, was constantly involved in the activation reaction during stress. It was therefore decided to study the contribution of MRF to the formation of the character of electrical activity of the brain and, in particular, of its hypothalamic formations which are ultimately responsible for hormonal secretion (and, consequently, for supplying the body with hormones under conditions of chronic emotional stress), and also to determine how closely the functional state of the thyroid gland and adrenal cortex is linked with MRF activity under conditions of stress. Information available on this subject is very contradictory and was obtained mainly by acute experiments [3-6, 8, 9, 12-15].

EXPERIMENTAL METHOD

Chronic experiments were carried out on nine cats weighing 3.0-3.5 kg using a model of combined stress caused by immobilization for 4 h accompanied by aperiodic electrodermal stimulation (EDS) of above-threshold strength. The series consisted of four experiments, carried out daily for 1 week. The EEG was recorded on a 17-channel Nihon Kohden (Japan) electroencephalograph by the method described in [1]. MRF was coagulated at coordinates Fr = 2.0, L = 3.5, H = 2.5 of the stereotaxic atlas [7] by a direct current of 1.5-2.0 mA passed for 2 min. The experiments were begun 2-3 weeks after the operation. After the end of the experiments the positions of the recording electrodes were verified histologically. Hormone concentrations were determined by radioimmunochemical assay in blood plasma taken through a

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[Presented by Academician of the Academy of Medical Sciences of the USSR A. M. Chernukh (deceased).] Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 96, No. 8, pp. 16-21, August, 1983. Original article submitted October 28, 1982.

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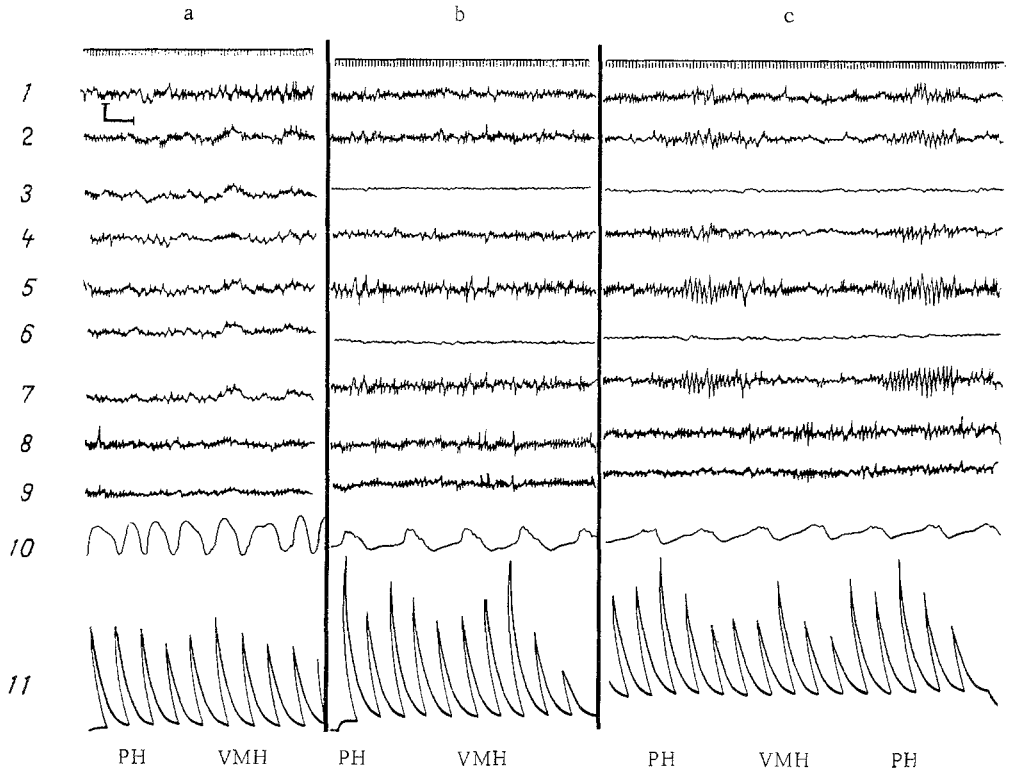

Fig. 1. Time course of changes in spontaneous EEG of cat before (a) and after (b, c) coagulation of MRF. Here and in Figs. 2 and 3, from top to bottom: hippocampus, septum, right MRF, amygdala, posterior hypothalamus (PH), left MRF, ventromedial hypothalamic nucleus (VMH), frontal cortex, sensomotor cortex, respiratory movements, analysis of EEG rhythms. Calibration: 50 μV, 1 sec.

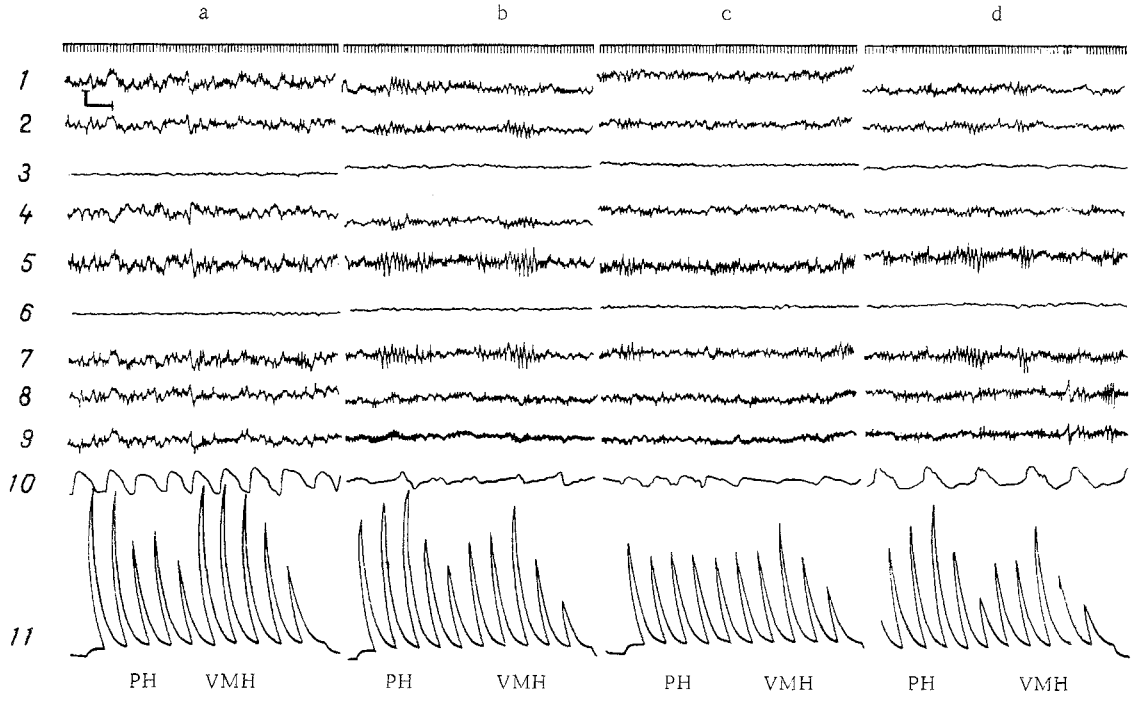

Fig. 2. Time course of changes in cat EEG during immobilization with EDS after bilateral coagulation of MRF (on 4th day). a) 5 min after presentation of 1st series of EDS; b) 20 min after 1st series of EDS; c) 5 min after presentation of 3rd series of EDS; d) 1 h after end of experiment.

TABLE 1. Plasma Levels of Cortisol (in μg%) and Thyroxine (in ng/ml) of Cats during Chronic

Hormone	Day of experiment							
	1st				2nd			
	background	after beginning of expt. 1 h	after beginning of expt. 4 h	after-period	background	after beginning of expt. 1 h	after beginning of expt. 4 h	after-period
Cortisol: before coagulation of MRF (n = 7)	1,61±0,23	6,44±0,92	9,01±1,40	2,64±0,93	2,45±0,46	6,46±0,97	6,27±0,74	2,66±0,52
P	—	<0,001	<0,001	>0,5	<0,2	<0,001	<0,001	<0,2
after coagulation of MRF (n = 5)	1,53±0,20	3,80±0,65	2,20±0,14***	2,36±0,47	2,12±0,70	3,57±0,69*	2,68±0,55	1,68±0,32
P	—	<0,02	<0,05	<0,2	<0,5	<0,05	<0,1	<0,5
Thyroxine before coagulation of MRF (n = 9)	21,8±1,6	35,6±4,4	35,0±2,8	34,0±6,1	32,0±5,3	33,8±3,8	37,3±3,6	33,3±3,8
P	—	<0,01	<0,01	<0,1	<0,1	<0,02	<0,01	<0,05
after coagulation of MRF (n = 5)	20,7±2,4	22,8±3,2	21,6±2,2	23,0±2,2	22,7±5,8	22,8±2,5	23,4±3,5	20,2±4,8
P	—	<0,5	<0,5	<0,5	<0,5	<0,5	<0,5	<0,5

Legend. Difference between response before and after coagulation of MRF: *P < 0.05, **P <

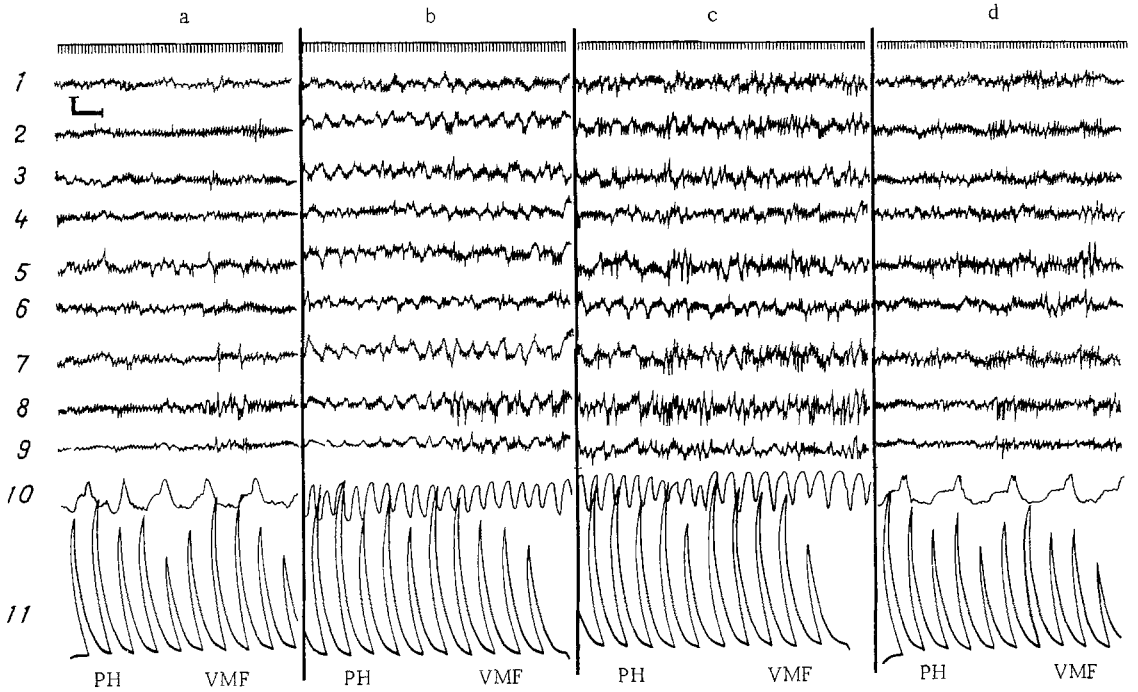

Fig. 3. Time course of changes in cat EEG during immobilization with EDS (on 4th day). a) Spontaneous EEG, b) 5 min after presentation of 1st series of EDS, c) 5 min after 3rd series of EDS, d) 1 h after end of immobilization.

catheter inserted previously into the jugular vein. Thyroxine was determined with the aid of special Res-O-Mat T_4 and Corning kits according to the instructions supplied. Cortisol was determined by the method of competitive binding with proteins, in which transcortin from human retroplacental plasma [11] was used as the binding component (cortisol was determined by V. I. Vorontsov and Yu. V. Polyntsev). The numerical results were subjected to statistical analysis.

Emotional Stress before and after Bilateral Coagulation of MRF (M ± m)

Day of experiment								
3rd				4th				2nd day after end of experiment
background	after beginning of expt.		after-period	background	after beginning of expt.		after-period	
	1 h	4 h			1 h	4 h		
2,36±0,40	6,41±0,34	7,44±1,01	2,84±0,48	2,67±0,25	5,91±0,68	5,40±0,74	3,50±0,52	3,00±0,80
<0,2	<0,001	<0,001	<0,05	<0,01	<0,001	<0,001	<0,001	<0,05
1,58±0,41 <0,5	3,44±0,80** <0,05	2,00±0,17 <0,2	2,10±0,27 <0,2	2,07±0,41 <0,5	3,20±0,19** <0,001	2,94±0,08** <0,001	2,13±0,25 <0,1	1,75±0,10 <0,5
31,5±4,1 <0,05	32,3±3,4 <0,02	34,3±3,3 <0,05	32,3±4,1 <0,05	28,4±2,6 <0,05	32,3±3,4 <0,02	33,0±3,7 <0,02	31,8±3,6 <0,05	31,3±3,2 <0,05
22,4±2,3 <0,5	21,7±3,0 <0,5	24,6±3,8 >0,5	21,8±3,9 <0,5	19,0±3,7 <0,5	21,0±4,3 <0,5	21,4±3,3 <0,5	17,3±1,5 >0,5	17,6±2,5 >0,5

0.02, ***P < 0.01; n) number of determinations.

EXPERIMENTAL RESULTS

Background electrical activity of the cortex and deep brain structures was recorded in unrestrained animals for 4-5 days. Since the animals had been accustomed beforehand to the experimental situation, their background EEG traces were quite stable. Total electrical activity was recorded in deep brain structures, with a uniform distribution of both slow and fast waves. Meanwhile in the sensomotor cortex high-frequency low-amplitude discharges as a rule predominated (Fig. 1a). After coagulation of MRF the character of spontaneous EEG activity changed sharply, the relative contribution of α-like waves increased considerably in all structures, and cycles of spindle activity often appeared and spread to all brain formations recorded (Fig. 1b, c). The animals' behavior also changed: they became quiet and their movements were considerably restricted. By contrast with the preoperative period, in the restraining cage throughout the experiment they showed no signs of restlessness, and even their response to EDS was of short duration; it ended soon after the end of stimulation, without the formation of a state of prolonged excitation (as shown by the quiet pneumogram and EEG). Correspondingly the EEG activation reactions to EDS were shorter than those of intact animals. The clearest electroencephalographic responses were recorded on the 1st and 4th days of the experiment. At these times of the experiment, by contrast with the 2nd and 3rd days, the longest activation reactions were observed in response to EDS with a mixed rhythm, so that the σ-rhythm dominated in some structures and in others the power of the discharges of all waves was increased. For instance, on the 1st day of the experiment of the first series EDS evoked a general activation reaction with an increase in power of the discharges mainly in the slow wave range. In the course of 10-15 min after the end of stimulation the relative contribution of α-like activity increased and the character of the EEG approximated to the background pattern, sleep spindles reappeared in it, but the cortical regions remained activated. In the next series of EDS the EEG activation reaction was more moderate and less prolonged. Immediately after it sleep spindles reappeared and spread to all brain structures and were recorded during 1 h of observation under unrestrained conditions (Fig. 2). Comparison of the data with reactions obtained in the same animal before coagulation of MRF in similar experiments shows the contribution of MRF to the organization of electroencephalographic responses to stress. It will be clear from Fig. 3 that in the intact animal short-term cycles of hypersynchronized activity were actually recorded in the intact animal in the spontaneous EEG on the 4th day of the experiment, indicating the manifestation of "static" excitation formed during the previous days of stress. In response to EDS a prolonged hypersynchronization reaction developed, with frequent epileptiform discharges and predominance of the σ-rhythm. Activity of this kind also was recorded in unrestrained animals (Fig. 3) 2 days after the end of the experiment, evidence of reinforcement of the stress re-

action during the after-period [1]. The hormonal secretion of the thyroid gland and adrenal cortex in animals undergoing the operation also differed similarly from that in the intact animals. In the latter, during chronic emotional stress, the plasma levels of both corticosteroids and thyroxine were raised significantly throughout the experiment. As Table 1 shows, the hormone levels also remained high during the after-period (2 days after the end of the experiments, during normal behavior). Changes in hormonal secretion described above correlated with the state of CNS function. After coagulation of MRF the thyroid did not respond to stress stimuli, and the level of thyroxine secretion correspondingly showed no significant change during 4 days of exposure to stress and in the after-period. The content of this hormone varied within physiologically normal limits (Table 1). A different pattern was found with regard to adrenocortical function. The duration of its response was remarkably inconstant. On certain days of the experiment (1st and 4th) the blood plasma corticosteroid level was significantly high during the experiment. On the 2nd and 3rd days, significant changes were found only during the first hour. During the after-period, 1 h and 2 days after the end of the experiments, the plasma corticosteroid level did not change significantly. Comparison of the response of the adrenal cortex to the experimental procedures in intact animals and after coagulation of MRF revealed significant differences throughout the 4 days of the experiment at all time intervals, evidence of a lower level of secretion in the latter.

These experiments showed a high degree of association between the state of the CNS function and hormonal secretion, with strict correlation between emotional state and the level of adrenocortical and thyroid hormone secretion.

Meanwhile the activating role of MRF in CNS activity and, what is particularly important, its role in the maintenance of a high functional state of hypothalamic structures responsible for secretion of releasing factors, were clearly demonstrated in them. After coagulation of MRF, although the animals responded to stress stimuli, the excitation which developed was abortive in character and did not reach the intensity required to increase thyroid function. So far as the adrenal cortex is concerned, even slight fluctuations in the surrounding medium can alter its secretion [10]. In the previous study [2], just as in the present, this property of the adrenal cortex was manifested to the full, evidence of the higher reactivity of the pituitary-adrenal system than of the pituitary-thyroid system.

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