NEUROPHYSIOLOGICAL ANALYSIS OF THE MECHANISM OF ENDOCRINE AND HYPERTENSIVE REACTIONS DURING CHRONIC EMOTIONAL STRESS

M. G. Amiragova, M. I. Arkhangel'skaya, Yu. V. Polyntsev, and V. I. Vorontsov

UDC 616.12-008.331.1-02: 616.433-008.6-02: 613.863

KEY WORDS: emotional stress; hypertensive vascular reactions; hormonal secretion.

According to the neurogenic theory of essential hypertension [4, 6, 8, 10] the principal pathogenic factors of development of the disease include long periods of emotional stress, to which, as the writers showed previously [1-3], the body responds by complex changes in nervous and endocrine reactions, which together constitute the neuroendocrine control system. Meanwhile the initial factors of the stress reaction, leading to the formation of hypertensive states, have not yet been explained. A neurophysiological analysis of the formation of endocrine and hypertensive reactions during chronic emotional stress was therefore indicated.

In the investigation described below the functional state of the CNS was investigated by comparison with peripheral vascular and hormonal effects during the development of emotional stress.

EXPERIMENTAL METHOD

Chronic experiments were carried out on 9 cats weighing 3-3.5 kg on a model of immobilization stress with electrodermal stimulation (EDS), designated combined stress. Full details of the technique were described previously [1]. EDS with the following parameters was applied at random intervals to the limb of the immobilized animal: voltage 40-60 V, pulse duration 1 sec. Every hour ten pulses were applied in the course of 10 min. The experimental series consisted of four experiments, conducted for 5 h daily. Blood pressure (BP) was recorded by a pressure transducer (Elena Schönander, Sweden) in the carotid artery, through a catheter implanted into it. Blood for hormone assay was taken through a catheter introduced into the jugular vein. Blood was taken before the experiment, 1 and 4 h after its beginning, and 1 h after its end, outside the experimental chamber. The total thyroxine concentration in the blood serum was determined with the aid of Res-O-Mat T_4 kits (Byk-Malinckrodt, West Germany) according to instructions issued by the firm. Cortisol and corticosterone were determined in the blood serum by competitive binding with proteins, and transcortin from retroplacental human plasma was used as the binding component [13]. Electrodes were implanted with the aid of a sterotaxic apparatus into the ventromedial, lateral, and posterior hypothalamic nuclei, the dorsal hippocampus, medial nucleus of the septum and amygdaloid complex, mesencephalic reticular formation, and also into the sensomotor and frontal regions of the cerebral cortex. Deep electrodes were oriented according to an atlas of the cat brain [12]. The location of the electrodes was verified histologically [14] and their position in brain structures was identified by reference to maps in the atlas [12]. Brain electrical activity was recorded on a 17-channel polygraph (Nihon Kohden, Japan). Frequency analysis of the electroencephalograms (EEG) was undertaken by means of a two-channel wide-band integrator, from the same firm. The pneumogram was recorded by means of a carbon transducer.

EXPERIMENTAL RESULTS

A background trace of the EEG of cortical and deep brain structures and the pneumogram during unrestrained behavior are shown in Fig. 1a. Electrical activity with uniform distribution of both slow and high-frequency waves was recorded in the deep brain structures. Meanwhile high-frequency low-amplitude discharges predominated in the cortex, as a rule. The background hormone levels studied (Table 1) and BP did not exceed the limits of the usual normal variations.

Laboratory of Neuroendocrine Regulation, P. K. Anokhin Institute of Normal Physiology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR G. N. Kryzhanovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 100, No. 8, pp. 153-157, August, 1985. Original article submitted December 21, 1984.

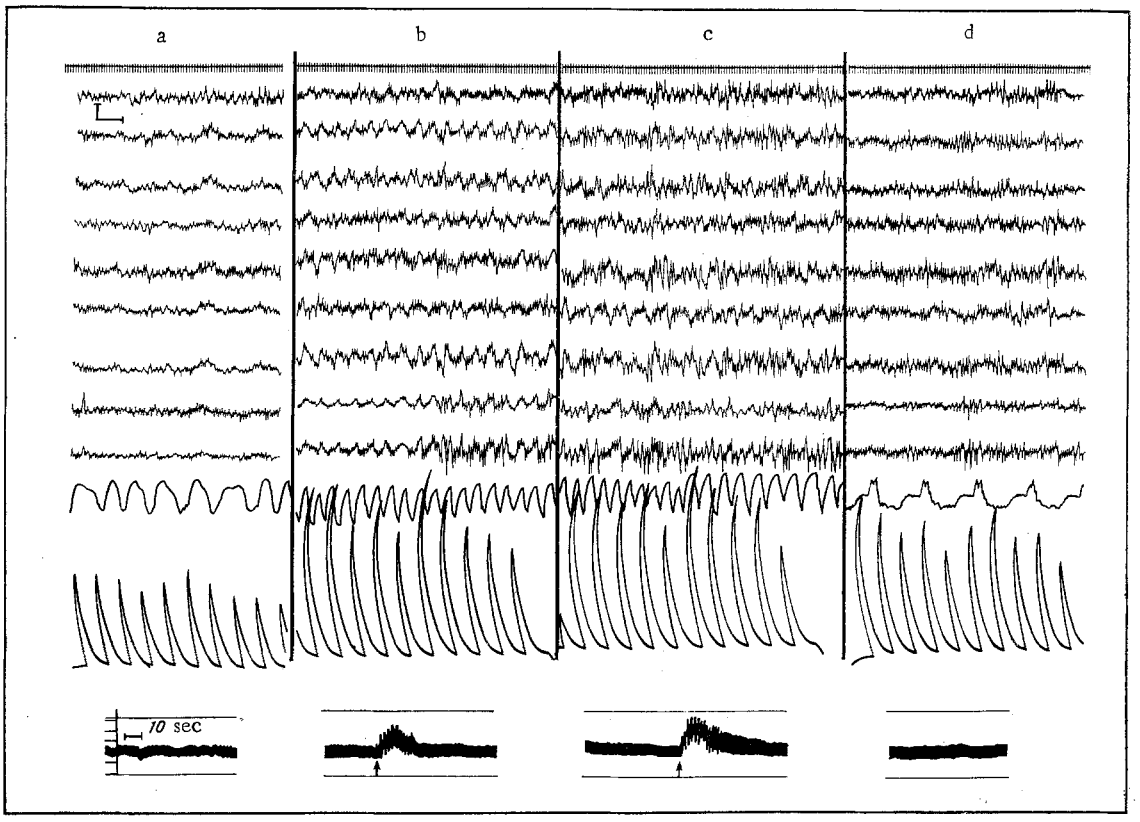

Fig. 1. Dynamics of changes in EEG and BP of a cat during immobilization with EDS (first day of stress): a) background trace; b, c) 1 and 4 h respectively after beginning of exposure to stress; d) 1 h after end of exposure to stress. From top to bottom: dorsal hippocampus, medial septal nucleus, left mesencephalic reticular formation, right mesencephalic reticular formation, medial nucleus of amygdaloid complex, posterior hypothalamic nucleus, ventromedial hypothalamic nucleus, frontal cortex, sensomotor cortex, pneumogram, trace of frequency analysis of EEG (calibration 50 μV, 1 sec), time course of change in BP. Arrows indicate times of application of EDS.

High-amplitude sharp-pointed slow waves appeared 1 h after the beginning of the experiment (Fig. 1b), and by the 4th h of the experiment (Fig. 1c) they became dominant in all the structures examined. Respiration was considerably quickened, the blood hormone levels were raised (Table 1), and an increase in amplitude and duration of the vascular reactions to EDS was observed.

After the end of the experiment, under conditions of unrestrained behavior, when the animal was quiet (Fig. 1d) BP returned close to the background level (135 mm Hg). The functional state of the CNS was depressed compared with the previous period, but the EEG of the recorded structures (especially hypothalamic formations) demonstrated their high activity (Fig. 1d), maintaining high blood hormone levels (Table 1).

Definite after-effects could thus be observed 1 h after the end of the first day of stress in both the neuroendocrine and the vascular systems.

During repetition of the experiments on the 2nd and 3rd days periods of synchronization in the EEG increased in both frequency and duration. These phenomena were most marked on the 4th day of the experiment, when quite considerable periods of "bursting" slow wave activity were recorded on the background EEG (Fig. 2a). Throughout the experiment paroxysmal activity did not disappear but was still present 1 h after the end of the experiment (Fig. 2). In all the structures analyzed slow rhythms, especially the θ-rhythm, predominated. The cortisol and thyroxine concentrations were significantly raised both in background blood samples taken in the animal house and throughout the experiment and in the after-period (1 h after the end of the experiment, under unrestrained behavioral conditions). The corticosterone level was significantly raised only during the experiment, and in the after-period and in the initial state only a tendency toward its rise could be noted. The background BP level at this time was raised, to 160/90 mm Hg (Fig. 3). Changes in the character of the vascular response to EDS will be noted: It immediately became prolonged (Fig. 3). BP, having risen in response

TABLE 1. Concentrations of Thyroxine (in ng/ml), Cortisol (in μg%), and Corticosterone (in μg%) in Peripheral Blood during Chronic Emotional Stress (M ± m)

Time of investigation	Thyroxine (n=9)	P	Cortisol (n=7)	P	Corticosterone (n=5)	P
			Cortisol (n = 7)			
Background	21,8±1,6	—	1,6±0,2	—	0,54±0,2	—
After beginning of experiment						
1 h	35,6±4,4	<0,01	6,4±0,8	<0,001	2,25±0,7	<0,05
4 h	35,0±2,8	<0,01	9,0±1,4	<0,001	2,45±0,9	<0,05
After-period	35,1±6,1	<0,1	2,6±0,9	<0,5	0,67±0,3	<0,5
			4th day of stress			
Background	28,4±2,6	<0,05	2,7±0,2	<0,01	0,92±0,3	<0,5
After beginning of experiment						
1 h	32,3±3,4	<0,02	5,9±0,7	<0,001	2,18±0,4	<0,05
4 h	33,0±3,7	<0,02	5,4±0,6	<0,001	1,9±0,6	<0,05
After-period	31,8±3,6	<0,05	3,5±0,5	<0,001	1,14±0,3	<0,5

Legend. P compared with background on first day of stress; n) number of determinations.

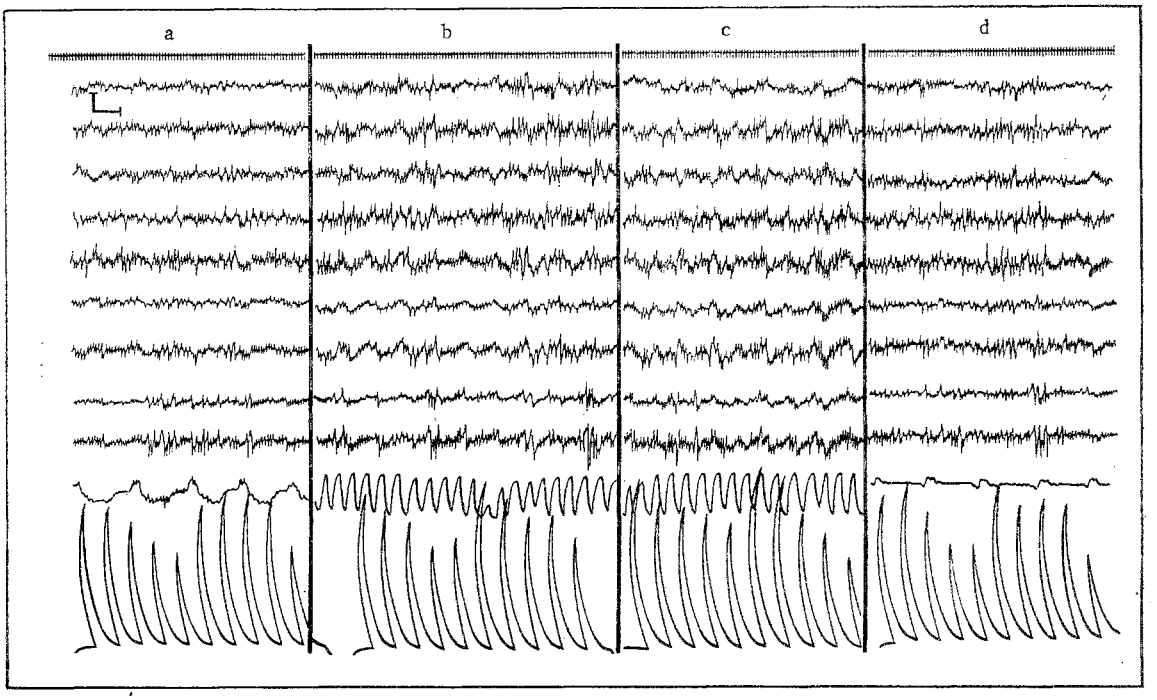

Fig. 2. Time course of changes in EEG of cat during immobilization with EDS (4th day of stress). From top to bottom: dorsal hippocampus, medial septal nucleus, mesencephalic reticular formation, medial nucleus of amygdaloid complex, posterior hypothalamic nucleus, lateral hypothalamus, ventromedial hypothalamic nucleus, frontal cortex, sensomotor cortex, pneumogram. Remainder of legend as to Fig. 1.

to EDS, had not fallen below 190/110 mm Hg even 1 h after the end of the experiment. The diastolic pressure also remained stable and high during unrestrained behavior in this case. As further tests showed, high values of BP (175/130 mm Hg) were recorded 3 days after the end of all the experiments. Not only the systolic, but also the diastolic pressure was raised at this time, evidence of increased peripheral resistance. Blood levels of both cortical and thyroxine remained significantly high under these circumstances.

The subsequent time course of the vascular and hormonal reactions was particularly interesting. On the 7th day after the end of the experiment only a tendency was noted for the blood hormone level to remain high, whereas BP was 30 mm Hg above the initial background value. This fact was later (1 month after the end of the experiment) subjected to more detailed analysis. This showed that even at this stage the functional state of the cortical and deep brain structures and the blood hormone levels (cortisol 1.30±0.1 μg, thyroxine 21.6±2.1 ng/ml) were normal whereas BP remained elevated and reached 160/120 mm Hg.

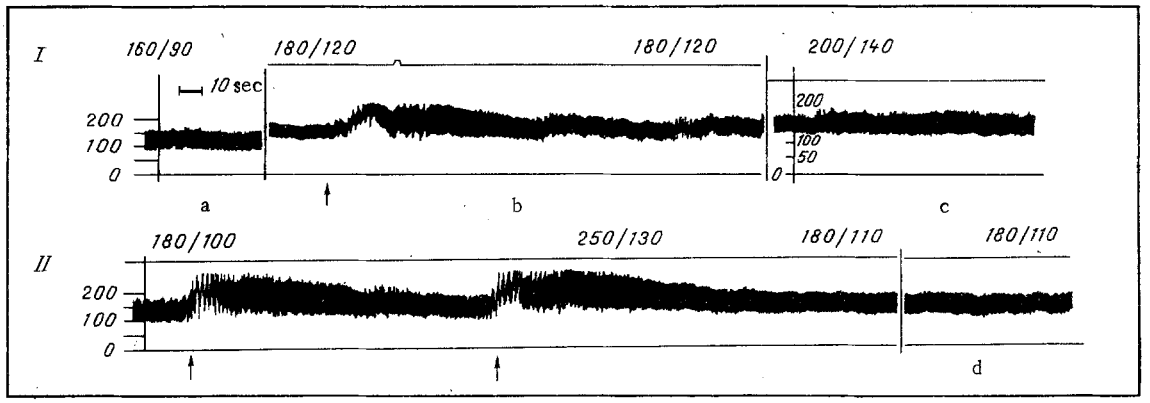

Fig. 3. Time course of changes in BP (in mm Hg) of cat exposed to immobilization with EDS (primary stress, 4th day): I) first day after beginning of stress: a) background; b) EDS; c) after 1st series of EDS; II) 4 h after beginning of stress: d) 1 h after end of stress. Arrow – EDS. Numbers – BP level.

The experiments thus showed that the association between disturbance of neuroendocrine mechanisms and BP changes in the initial phase of stress is no longer observed during the late after-period, for neuroendocrine functions are restored to normal before hemodynamic reactions. At the same time, one very important phenomenon, which we found in the course of this repeated series of stress, deserves attention. As early as in the first hour of the first day of the repeated series of stress, against the background of normal EEG activity, stable hypersynchronized activity of the slow high-amplitude sharp-pointed waves developed, and during subsequent exposure of the animal to stress, it became "static" in character. By contrast with the first series of exposures to stress, the neurophysiological manifestations of repeated stress were no longer phasic in character, but were formed immediately into long-term pathological excitation, involving all the brain structures investigated. This was accompanied by high hormonal secretion. Vascular reactions to EDS also were prolonged from the beginning, resembling the responses on the 4th day of the first series of stress.

The facts described above indicate that previous exposure of the animal to stress led to the development of persistent hypersensitivity of the pressor mechanisms of the body. As a result of reorganization of neuroendocrine and neurohumoral regulatory mechanisms, the actual substrate of regulation is changed, namely the vessel wall: Its reactivity to substances circulating in the blood stream is enhanced [7, 9, 11].

The possibility likewise cannot be ruled out that, as Anokhin considered, "the qualitative transition from dynamic neurophysiological states to metabolic stabilization of hyperfunction, with the involvement of ribonucleic acids and specific protein formations" [5] facilitates reinforcement of the pathogenetic complex of hypertension.

Considering the facts described above, it can be postulated that these results, obtained in the late after-period, when normal electrographic and hormonal responses were restored, reflect metabolic shifts in the neuronal formations of the CNS that play a particularly important role in the regulation of vascular reactions, and this factor, together with peripheral vascular mechanisms, is responsible for stabilizing the hypertensive state.

Thus it is the process of formation of hypertension in animals during chronic emotional stress that is brought about by dynamic changes in the state of function of the CNS, including the neuroendocrine control system. These changes can be divided conventionally into two stages.

The first stage is characterized by the appearance of short cycles of hypersynchronized activity, affecting all the structures studied; this is accompanied by activation of hormonal secretion not only by the adrenal cortex, but also by the thyroid gland, evidence that the factors to which the animal is exposed are highly significant for it [2]. Vascular reactions to EDS are characterized by transient effects. In this stage self-regulation of BP is still undisturbed.

During the second stage (3rd and 4th days of stress) "static" excitation is formed in the CNS, and the blood hormone levels remain significantly raised. Vascular reactions to EDS become particularly prolonged in character, self-regulation of BP is disturbed, and it is stabilized at a high level for a long time.

LITERATURE CITED

1. M. G. Amiragova and M. I. Arkhangel'skaya, Byull. Eksp. Biol. Med., No. 6, 24 (1982).
2. M. G. Amiragova, M. I. Arkhangel'skaya, and V. I. Vorontsov, Byull. Eksp. Bill. Med., No. 6, 9 (1983).
3. M. G. Amiragova and M. I. Arkhangel'skaya, Byull. Eksp. Biol. Med., No. 8, 16 (1983).
4. P. K. Anokhin, Vestn. Akad. Med. Nauk SSSR, No. 6, 10 (1965).
5. P. K. Anokhin, in: Abstracts of Proceedings of the 21st Session of the General Assembly of the Academy of Medical Sciences of the USSR [in Russian], Moscow (1965), pp. 3-5.
6. P. K. Anokhin, Biology and Neurophysiology of the Conditioned Reflex [in Russian], Moscow (1968).
7. A. A. Dzizinskii and I. Sh. Shterentalish, in: Neurohumoral Mechanisms of Arterial Hypertension [in Russian], Novosibirsk (1978), pp. 64-80.
8. G. F. Lang, Essential Hypertension [in Russian], Leningrad (1950).
9. Kh. M. Markov, Pathophysiology of Arterial Hypertension [in Russian], Sofia (1970).
10. A. L. Myasnikov, Essential Hypertension [in Russian], Moscow (1954).
11. J. Genest, W. Novaczynski, R. Boucher, et al., Can. Med. Assoc. J., 118, 538 (1978).
12. H. M. Jasper and C. Ajmone-Marsan, A Stereotaxic Atlas of the Diencephalon of the Cat, Ottawa (1954).
13. B. Murphy, J. Clin, Endocrinol., 27, 973 (1967).
14. F. C. Muzman, M. Alcaraz, and A. Fernandez-Guardiola, Bol. Estud. Med. Biol. (Mex), 16, 29 (1959).
15. M. Schalkamp, G. Wenting, and A. Veld, Clin. Endocrinol., 10, 397 (1981).