BRAIN CATECHOLAMINES IN THE EARLY STAGE OF EMOTIONAL STRESS

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To study central neurochemical mechanisms leading to a disturbance of self-regulation of the arterial blood pressure (BP) under conditions of emotional stress the dynamics of BP and the catecholamine level in different parts of the brain were studied in August and Wistar rats after immobilization for 2 h. The BP level was virtually indistinguishable from normal throughout the experiment. The catecholamine concentration in the hypothalamus, mesencephalon, the region of the isthmus cerebri, and the medulla was significantly changed. It is suggested that the mechanism of the changes in catecholamine concentration during stress in rats of both strains is similar in the region of the hypothalamus and medulla. Activity of the noradrenalin-synthesizing neurons of the isthmus cerebri and of the dopamine-synthesizing neurons of the mesencephalon in the rats of these two strains, however, is specific, and that is evidently one of the factors responsible for differences in the resistance of cardiovascular functions in the later stages of immobilization.

KEY WORDS: emotional stress; brain catecholamines; arterial blood pressure; locus coeruleus.

According to Anokhin's theory of functional systems, the stability of normal physiological functions is determined by mechanisms of self-regulation [1]. In emotional stress self-regulation of physiological functions is disturbed, but the degree of the disturbance differs in rats of different lines. For instance, during prolonged immobilization in August rats the arterial blood pressure (BP) and the heart rate change in 90% of cases, whereas in Wistar rats they do so in only 48% of cases [3, 4].

Accordingly, in order to study the central neurochemical mechanism determining resistance of the body to emotional stress, it is interesting to study the neurochemical changes in the brain in consecutive stages of emotional stress. In the investigation described below the dynamics of catecholamines and BP was studied in the initial stage of immobilization stress.

EXPERIMENTAL METHOD

Experiments were carried out on male August and Wistar rats (five and six animals respectively) weighing 200-250 g. The animals were immobilized in soft gauze. BP was measured by the direct method on the Mingograph-34. Under ether anesthesia, 24 h before the experiment a catheter was introduced through the caudal artery of the rats into the thoracic part of the descending aorta. BP was recorded every 15 min continously for 1-2 min. The animals were decapitated after immobilization for 2 h. The noradrenalin and dopamine concentrations were determined [7] on a Hitachi MPF-2A spectrofluorometer in the emotiogenic zones of the brain and in structures with a high concentration of biogenic amines, namely the hypothalamus, the oral portion of the mesencephalon at the level of the superior colliculus (the region of concentration of bodies of dopamine-synthesizing neurons), the regions of the isthmus cerebri with the adjacent caudal portion of the mesencephalon (the location of the cell bodies of noradrenalin-synthesizing neurons – the locus coeruleus), and the caudal portion of the medulla (the location of adrenalin-synthesizing neurons). The samples weighed 40-60, 50-70, 90-110, and 60-80 mg respectively. Intact rats, and also animals into which a catheter was introduced, but which were kept under conditions of free behavior (in a large cage) served as the control.

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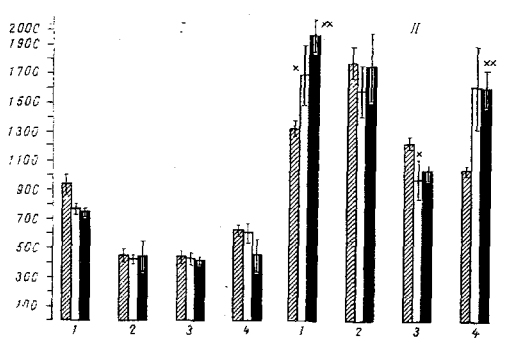

Fig. 1

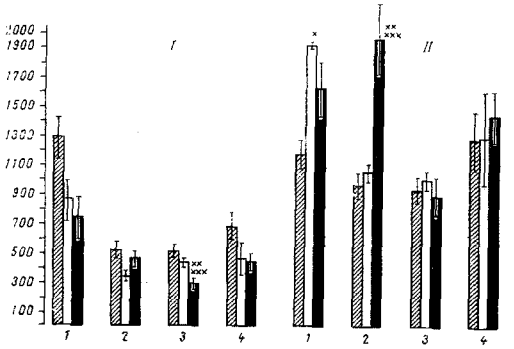

Fig. 2

Fig. 1. Concentrations (in ng/g tissue) of noradrenalin (I) and dopamine (II) in different parts of brain of August rats after immobilization for 2 h. 1) Hypothalamus; 2) oral portion of mesencephalon at level of superior colliculus; 3) region of isthmus cerebri with adjacent caudal portions of medulla. Obliquely shaded column represent normal state; unshaded column operative controls; black column experiment. $P < 0.05$: ×) comparison of normal with operative control, ××) comparison of normal with experiment, ×××) comparison of operative control with experiment.

Fig. 2. Concentrations of noradrenalin and dopamine (in ng/g tissue) in different parts of brain of Wistar rats after immobilization for 2 h. Legend as in Fig. 1.

TABLE 1. Values of DA/NA Index in Different Parts of Rat Brain under Normal Conditions, after Introduction of Catheter (operative control), and after Immobilization for 2 h

Part of brain	August rats			Wistar rats		
	normal	operative control	expt.	normal	operative control	expt.
Hypothalamus	1,3	2,2	2,6	0,9	2,2	2,2
Mesencephalon at level of superior colliculus	4,0	3,7	2,9	1,7	3,0	4,3
Region of isthmus cerebri	2,8	2,3	2,5	1,8	2,3	3,1
Medulla	1,6	2,6	3,5	1,9	2,8	3,2

EXPERIMENTAL RESULTS

In the course of observations lasting 2 h on immobilized rats of both lines no significant changes were found in BP relative to the original level. The mean BP of the Wistar rats at the beginning of the experiment was 115 ± 5 mm Hg and at the end of the experiment 114 ± 7 mm Hg; in the August rats it was 127 ± 4 and 125 ± 8 mm Hg respectively.

Concentrations of catecholamines in different parts of the brain of the August and Wistar rats after immobilization for 2 h, compared with the normal state and the operative control, are given in Figs. 1 and 2. The latter also was regarded as emotional stress, although milder than that caused by introduction of the catheter and subsequent immobilization.

Introduction of the catheter into Wistar rats evoked a sharper fall in the noradrenalin level than in the August rats, and the fall was intensified after immobilization. The dopamine concentration was increased to 165% of normal, possibly in connection with early involvement of dopamine-synthesizing neurons of the arcuate nucleus in response to stress [13]. The dopamine concentration in the August rats increased by a similar amount only after immobilization.

In the medulla of the Wistar rats the noradrenalin concentration after introduction of the catheter fell sharply to the characteristic level found during strong emotional stress; the noradrenalin concentration in the August rats fell only after immobilization. In August rats weak stress led to a sharp increase in the dopamine level, which was unchanged after immobilization; the dopamine level in the medulla of the Wistar rats was virtually unchanged.

Despite the different changes in the catecholamine concentrations in the medulla and hypothalamus, the dopamine/noradrenalin (DA/NA) ratio in rats of both lines changed in the same direction in response to stress (Table 1); this suggests that the mechanisms of catecholamine metabolism are similar in these parts of the brain.

When the changes in catecholamines in the medulla are analyzed it must be emphasized that two groups of adrenalin-synthesizing neurons are located in its caudal portion, which was chosen for study [9]; the ventral group, moreover, is located in the part of the medulla which, in physiological investigations [6], was defined as the region responsible for medullary control of BP. Accordingly it can be considered that changes in the catecholamine level in this region are due to its participation in the system for self-regulation of BP. Indirect evidence in support of this conclusion is given by the increase in activity of an enzyme of adrenalin synthesis during the development of hypertension of different etiology [15].

Activity of the dopamine-synthesizing neurons of the mesencephalon differed significantly in the rats of the two lines. In August rats, which are more predisposed than Wistar rats to disturbances of cardiovascular function, under normal conditions a higher dopamine level was found. This is in agreement with data obtained previously showing a high dopamine level and low dopamine-β-hydroxylase activity in spontaneously hypertensive rats and during the development of hypertension [14, 15]. The DA/NA ratio in August rats in a state of stress was virtually unchanged, whereas in Wistar rats a considerable increase in the ratio depending on the degree of stress was found.

The decrease in the noradrenalin concentration in the mesencephalon of Wistar rats after introduction of the catheter coincided with a sudden decrease in its concentration in the region of the isthmus cerebri, and may be attributable to weakening of the influence of the locus coeruleus on the dopamine-synthesizing neurons of the mesencephalon [5]. There is evidence that the locus coeruleus participates in the regulation of cardiovascular function – in the organization of the pressor response [8, 12, 14]. However, considering the universal intercerebral connection of the locus coeruleus with brain structures, each of which participates specifically in the mechanism of the various factors concerned in relations between the organism and its environment, it can tentatively be suggested that the pressor function, demonstrated on stimulation of the locus coeruleus, is only part of the activity of this formation. Its general role is evidently in the maintenance of homeostasis adequate for the situation, as is clear from experimental data [11], autopsy observations [2], and the results of ontogenetic investigations [10].

On the whole, as analysis of the results described above shows, the mechanisms of catecholamine metabolism are evidently similar in type in the hypothalamus and medulla of rats of the two strains chosen for investigation, at the stage of short-term stress before the appearance of disturbances of cardiovascular functions. The difference in the response of the mesencephalon and the region of the isthmus cerebri to emotional stress in August and Wistar rats (a sharp rise in the DA/NA ratio under conditions of stress in Wistar rats compared with only slight changes in August rats) suggests that the morphological and neurochemical features distinguishing these parts of the brain may be one of the main factors determining differences in the resistance of the cardiovascular functions to emotional stress arising during more prolonged immobilization.

LITERATURE CITED

1. P. K. Anokhin, Vestn. Akad. Med. Nauk SSSR, No. 6, 10 (1965).
2. E. S. Eletskii, Tr. Kafedry Nerv. Bolez. Saratov. Med. Inst., No. 7, 159 (1948).
3. Yu. G. Skotselyas, E. A. Yumatov, and E. M. Krokhina, in: Models and Methods for Studying Experimental Emotional Stresses [in Russian], Volgograd (1977), p. 275.
4. K. V. Sudakov, Emotional Stress and Arterial Hypertension [in Russian], Moscow (1976).
5. S. M. Antelman and A. R. Caggiula, Science, 195, 646 (1977).
6. F. R. Calaresu and M. R. Thomas, Brain Res., 87, 335 (1975).
7. R. H. Cox and I. R. Perhach, J. Neurochem., 20, 1777 (1973).
8. K. Fuxe, T. Hökfelt, P. Bolme, et al., in: Central Action of Drugs in Blood Pressure Regulation, Tunbridge Wells, England (1975).
9. T. Hökfelt, K. Fuxe, O. Johansson, et al., Eur. J. Pharmacol., 25, 108 (1974).
10. G. Jonsson, Exp. Neurol., 53, 801 (1976).
11. M. Jouvet, Science, 163, 32 (1969).
12. H. Kawamura, C. G. Gunn, and E. D. Frohlich, Brain Res., 140, 137 (1978).
13. R. Kvetnansky, A. Mitro, M. Palkovits, et al., in: Catecholamines and Stress (International Symposium), Oxford (1976), p. 39.

14. T. Nagatsu et al., in: Catecholamines and Stress (International Symposium), Oxford (1976), p. 47.
15. J. M. Saavedra, H. Grobecker, and J. Axelrod, Circ. Res., 42, 529 (1978).

ANALYSIS OF ANALGESIA EVOKED BY CREATION OF AN EXCITATION GENERATOR IN DORSAL RAPHE NUCLEUS

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An excitation generator was created in the dorsal raphe nucleus of the mesencephalon in experiments on albino rats by microinjection of tetanus toxin into the nucleus. During formation of the excitation generator electrical activity was found to change in this nucleus, with a sharp increase in the primary negative component (N_1) and a change in the general configuration of the evoked potentials (EP), and an increase in the frequency of spontaneous paroxysmal activity. These changes in EP coincide in time with the appearance of deep and increasing analgesia. The type of analgesia described is not abolished by naloxone.

KEY WORDS: Analgesia; excitation generator; tetanus toxin; evoked potentials; dorsal raphe nucleus.

The raphe nuclei of the midbrain and medulla play a specially important role in the central mechanisms of analgesia induced both by electrical stimulation of these nuclei and by injection of substances interacting with opiate receptors into them [1, 9-11, 14]. It was shown previously [4] that injection of tetanus toxin (TT), which disturbs inhibitory mechanisms and so evokes the formation of a generator of enhanced excitation [2-7], into the dorsal raphe nucleus of the midbrain leads to deep analgesia.

In order to continue the analysis of the mechanisms of this analgesia, it was decided to study evoked potentials in the dorsal raphe nucleus, into which TT was injected, and also to make a comparative analysis of the type of analgesia described above and that evoked by morphine.

EXPERIMENTAL METHOD

Experiments were carried out on 50 male albino rats weighing 200-300 g. Analgesia, determined by behavioral tests, was induced by microinjection of 1-3 MLD of purified TT in a volume of 0.05 ml, at a point whose coordinates were taken from the atlas [12]. Full details of the method were described previously [4]. Evoked potentials were recorded in the dorsal raphe nucleus before injection of TT and after the appearance of definite analgesia. Evoked potentials were derived in the usual way by a monopolar method with nichrome electrodes (diameter 0.2 mm) in glass insulation, connected to the micropipet for TT injection. The electrode and micropipet were inserted under hexobarbital anesthesia (100 mg/kg body weight). Processes to be recorded were photographed from the monitor screen of a BC-9 dual-beam oscilloscope (Japan) by means of a photorecorder. Nociceptive electrical stimulation was applied to the skin of the tail and limbs through needle electrodes from an ÉSU-1 stimulator. The positive and negative components of the evoked potential were assessed quantitatively and the experimental results subjected to statistical analysis. Experiments were carried out on rats hypophysectomized under ether anesthesia by a suction method through a burr-hole in the base of the skull (these experiments were carried out jointly with É. R. Bagramyan). Morphine was injected systemically (15 or 50 mg/kg body weight) or into the dorsal raphe nucleus (5 μg in 1 μl). Naloxone also was injected either systemically (0.1 mg/kg body weight) or into the dorsal raphe nucleus (5 μg in 1 μl).

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