The writer's previous experiments with application of MP to the sensomotor cortex of one hemisphere and threshold stimulation of the opposite cortex showed that combined stimulation of this kind likewise could not raise the level of excitation in the dispatch station to a sufficiently high degree to become determinant. Only as a result of subthreshold stimulation of the dispatch station did chronic changes develop in the CNS. They can evidently be explained by gradual summation of excitation in the sensomotor cortex. The appearance of a "flare-up" in these cases is regarded by many workers [7, 8] as a result of a change in the functional state of the cerebral cortex.

Stable chronic hyperkinesias could be obtained in animals subjected to a combination of subthreshold stimulation and MP. Investigations [1, 2] have shown that MP of the brain accelerates the formation and fixation of motor responses during learning, and subsequently these responses were preserved for a long time and could be reproduced by MP alone. The appearance of stable hyperkinesias in the case of direct action on the dispatch and destination stations can evidently be regarded as the result of functioning of a determinant dispatch station, characterized by a certain strength of excitation, and of the creation of a relatively stable pathological system, as defined by Kryzhanovskii [4].

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EFFECT OF HYPERACTIVATION OF THE LOCUS COERULEUS ON RHYTHM OF THE INTACT AND REACTIVELY CHANGED HEART

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UDC 616.12-008-02:616.831.85-008.61-092.9

KEY WORDS: locus coeruleus; generator of pathologically enhanced excitation; cardiac rhythm.

The locus coeruleus (LC), the principle nucleus of the dorsal noradrenergic pathway, is known to be closely connected with various formations of the nervous system, including structures participating in regulation of the circulation [3, 6, 8]. Preliminary coagulation of LC has been shown to considerably reduce disturbances of the cardiac rhythm in acute myocardial ischemia. It has been suggested that in this form of pathology LC may acquire the role of a hyperactive determinant structure [1].

Accordingly, in the present investigation the character of rhythmic activity of the intact heart and of a reactively changed heart was studied during electrical stimulation of LC with the creation of a generator of pathologically enhanced excitation (GPEE) in it [1].

EXPERIMENTAL METHOD

Experiments were carried out on 86 noninbred male rats weighing 200-240 g anesthetized with pentobarbital sodium (25 mg/kg) and artificially ventilated (succinylcholine 0.2 mg/kg).

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 96, No. 8, pp. 24-28, August, 1983. Original article submitted March 3, 1983.

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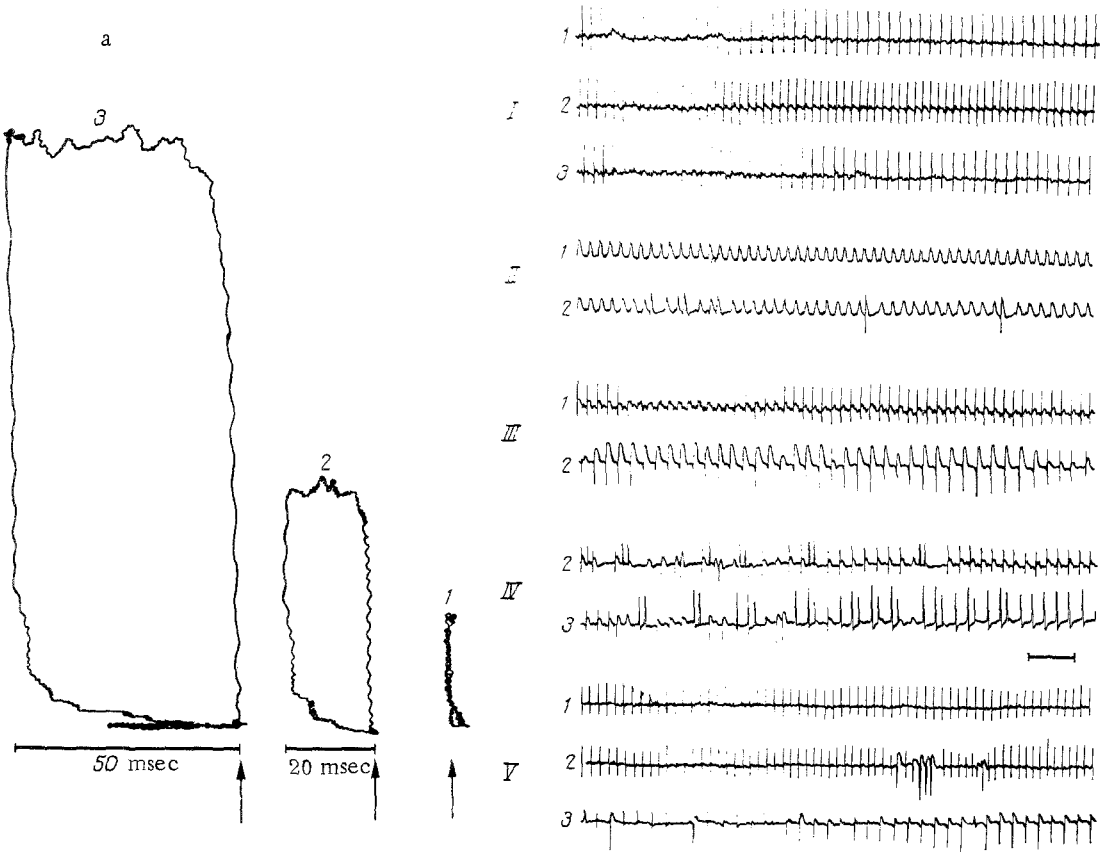

Fig. 1. Effect of electrical stimulation of LC on cardiac rhythm. a) Effect of electrical stimulation of LC on the normal heart. Parameters of stimulation: amplitude 10 V, frequency 1-25 Hz (1), 50 Hz (2), and 100 Hz (3). Recorded on x-y graph plotter: abscissa, integrated function of increase in heart rate (integration time 1 sec); ordinate, integrated function of stimulating pulses. Arrows indicate beginning of stimulation. Calibration lines — time of reduction of intervals. b) Effects of electrical stimulation of LC: I) normal heart; II, III, IV) acute myocardial ischemia; V) 10 min after injection of strophanthin. 1) Before stimulation, 2) during stimulation, 3) immediately after stimulation. ECG — lead II. Calibration — 1 sec.

Hyperactivation of LC was carried out by electrical stimulation (38 experiments) or by creation of a GPEE by microinjection of penicillin into the nucleus (48 experiments). Electrical stimulation was carried out on animals with a normal heart (n = 11), animals with acute myocardial ischemia (n = 8), with adrenalin-induced myocardial damage (n = 8), and after intravenous injection of strophanthin K (n = 11). During stimulation of LC (for 20 sec) bipolar nichrome electrodes, insulated with enamel except at the tip for 0.5 mm (diameter 50 μ each, interelectrode distance 100 μ) were used to transmit regular pulses with a frequency of 25-100 Hz, duration 1 msec, and amplitude 10-30 V. The electrodes were inserted in accordance with coordinates of a stereotaxic atlas [7]: A = 7.4, L = 1.0, H = 6.0.

Acute myocardial ischemia was induced by ligation of the lower third of the left anterior coronary artery 5 min before electrical stimulation. For this purpose, at the beginning of the experiment the ends of a ligature applied in the form of a loop to the coronary vessel, were brought out through the chest wall, and the vessel was occluded at the required time. Adrenalin myocarditis was induced by subcutaneous injection of adrenalin (7 mg/kg) one day before the experiment. Strophanthin K (460 μg/kg) was injected immediately before electrical stimulation of LC.

To create a GPEE in LC, 50 units of penicillin in a volume of 0.1 μl was injected into the nucleus through a micropipet by means of a microinjector. Rhythmic activity of the normal heart (n = 15), and of the heart with acute myocardial ischemia (n = 11), of adrenalin

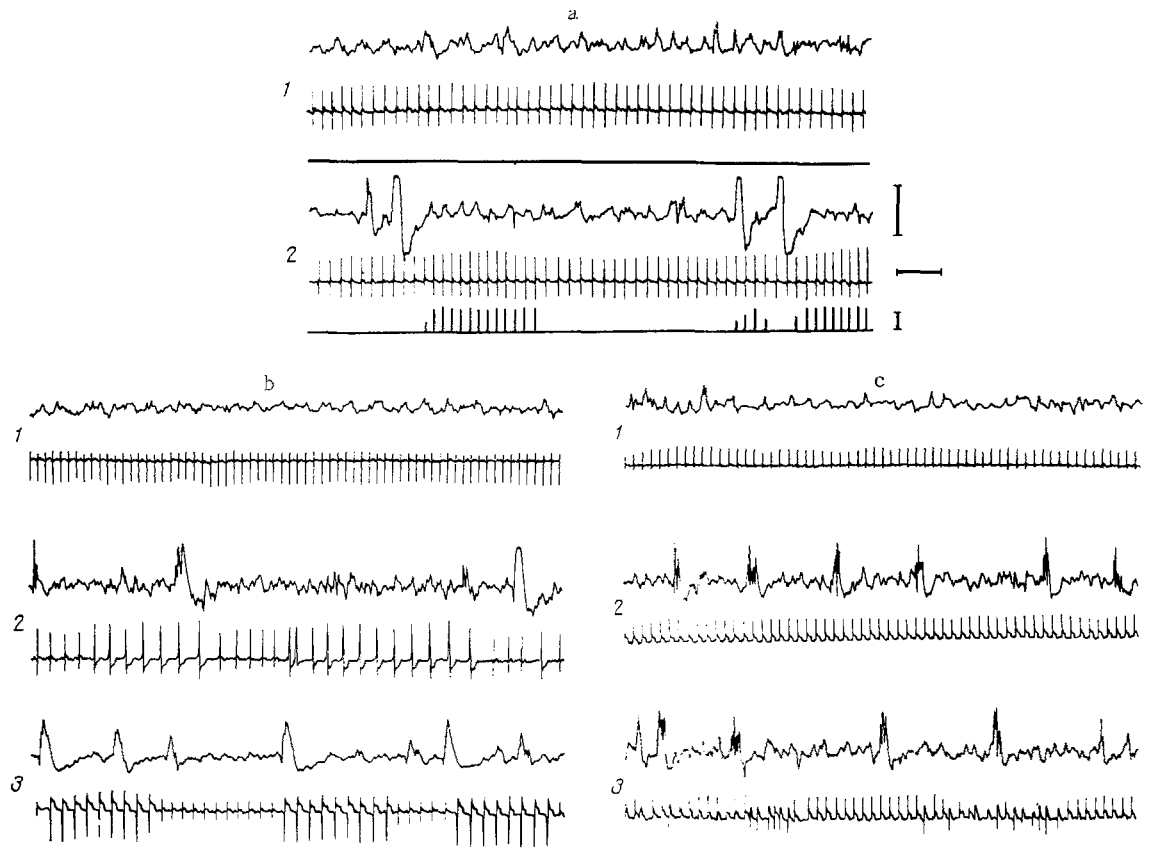

Fig. 2. Character of cardiac rhythm during hyperactivation of LC by creation of a GPEE in it with penicillin. a) Effect of GPEE on rhythm of normal heart. 1) Initial state, 2) 10 min after injection of penicillin into LC. Top traces — EA in LC, middle — ECG (lead II); bottom lines — markers of intervalograph, proportional to reduction of interval. b) Effect of stropanthin K on cardiac rhythm during hyperactivity of LC. 1) Initial state, 2) 5 min after injection of strophanthin K and 10 min after injection of penicillin into nucleus, 3) 10 min after injection of strophanthin K. c) Effect of acute myocardial ischemia on cardiac rhythm during hyperactivity of LC. 1) Initial state, 2) immediately after ligation of coronary artery and 10 min after injection of penicillin into nucleus, 3) 10 min after ligation of coronary artery. Calibration: top 250 μV; middle 1 sec; bottom 20 msec.

myocarditis (n = 11), and after intravenous injection of strophanthin K (n = 11) was studied against the background of induced hyperactivity of LC. Stereotaxic coordinates of injection of penicillin into the nucleus and the method of obtaining acute myocardial ischemia and adrenalin myocarditis, and the dose of strophanthin K were the same as in the experiments with electrical stimulation of LC.

In all series of experiments the animals' ECG was recorded in standard leads, and in the experiments with injection of penicillin, besides the ECG, electrical activity (EA) was recorded also in LC. For this purpose nichrome electrodes with enamel covering (thickness 50 μ, with the tip uninsulated for a distance of 0.5 mm) were used. ECG and EA in LC were recorded on a Bioscript cardiopolygraph and encephalograph. In some experiments EA in LC and the ECG were recorded on magnetic tape and subsequently processed on an x-y graph plotter. To study the effect of GPEE in LC on the rhythm of the normal heart, an RR interval analyzer also was used; its parameters were recorded on the Bioscript encephalograph simultaneously with EA in LC and the ECG.

The location of the electrodes and micropipets after each experiment was verified histologically in sections cut on a freezing microtome.

EXPERIMENTAL RESULTS

Electrical stimulation of LC in all experiments caused an increase in the rate of contraction of the normal heart with shortening of the RR interval by 20-55 msec (Fig. 1b). The

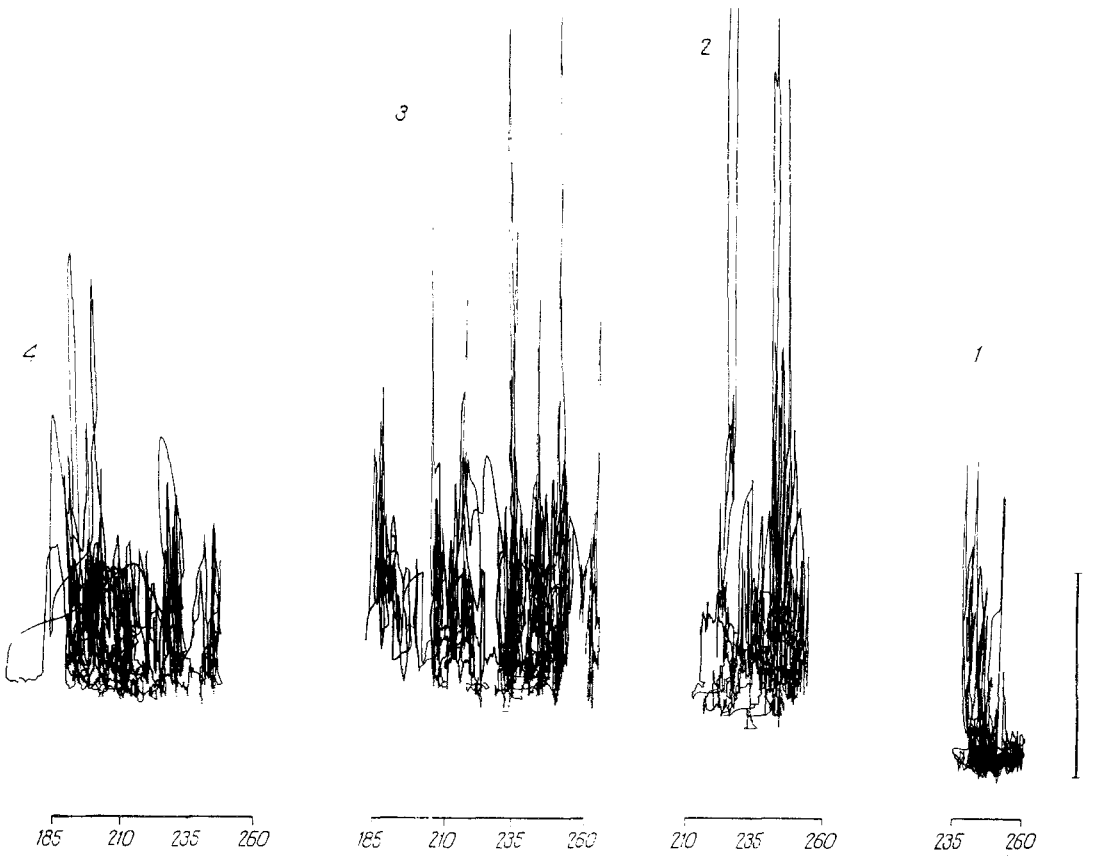

Fig. 3. Time course of changes in rhythm of intact heart and EA in LC after injection of penicillin into it. Integrated 5-min cuts of heart rate (abscissa) and EA in LC (ordinate) after injection of penicillin into LC: 1) immediately after injection, 2) 5 min, 3) 10 min, 4) 15 min after injection. Integration time 0.5 sec. Numbers below indicate RR intervals (in msec). Calibration 250 μV.

positive chronotropic effect observed was most pronounced after stimulation with a frequency of 100 Hz (Fig. 1, 3). The development of tachycardia usually began 2-3 sec after the beginning of stimulation and continued until its end. With the stopping of stimulation of LC the heart rate was quickly restored.

Different effects were observed during stimulation of LC in animals with acute myocardial ischemia. They were characterized by the appearance of a ventricular rhythm (Fig. 1, III) and of single (Fig. 1b, II) and grouped ventricular extrasystoles (Fig. 1b, IV). Frequently with the ending of stimulation these rhythm disturbances lasted longer — up to 15-20 sec (Fig. 1b, IV). Electrical stimulation of LC after injection of strophanthin K led only to brief arrhythmias. The most marked disturbances of the cardiac rhythm in the animals of this group developed in the poststimulation period, and against the background of considerable bradycardia they were polytopic in character (Fig. 1b, V). In the overwhelming majority of animals with adrenalin damage (in seven experiments) no disturbances of the cardiac rhythm were found either during or after stimulation of LC.

Injection of penicillin into LC induced generation of single high-amplitude seizure discharges after 1-2 min; their frequency and amplitude reached a maximum after 15-20 min, and after 1 h they were considerably reduced.

The appearance of seizure discharges in LC led to changes in rhythmic activity of the normal heart, in the form of transient periods of quickening of the cardiac rhythm with shortening of RR intervals (to 40-50 msec) to every discharge of the generator (Fig. 2a, 2). Phenomena of this kind began as a rule 5-10 min after injection of penicillin and were observed for 15-20 min (Fig. 3).

Injection of strophanthin K against the background of hyperactivity of LC induced by GPEE substantially modified the cardiac rhythm. In most experiments, starting with the 5th minute after injection of strophanthin K (10 min after microinjection of penicillin into LC) discharges of the generator in LC were accompanied by the appearance of an idioventricular rhythm, often with migration of ectopic foci (Fig. 2b, 2, 3). These disturbances of rhythmic activity were observed for not more than 10-15 min, despite continuing activity of the generator in LC.

The GPEE in LC induced the appearance of arrhythmias after ligation of the coronary artery also. Under these circumstances the frequency of appearance of single and grouped ventricular extrasystoles also correlated with the frequency of seizure discharges of the generator (Fig. 2c, 3). However, just as in the experiments with strophanthin K, these changes in the cardiac rhythm were of short duration (up to 7-12 min). The GPEE in LC did not affect the cardiac rhythm of animals with adrenalin-induced damage to the myocardium.

These investigations thus showed that hyperactivation of LC by its electrical stimulation or the creation of a GPEE led to disturbances of rhythmic activity of the heart of a similar type. Enhanced activity of LC caused changes of tachycardial type in the rhythm of the intact heart, accompanied by arrhythmias of various kinds when the intrinsic regulatory mechanisms of the heart were disturbed. The fact that disorders of the cardiac rhythm appeared some time after the beginning of stimulation of LC or the creation of a GPEE in it with the aid of penicillin, can be explained either by the need to activate humoral adrenergic influences or by the role of regional mechanisms of regulation of cardiac activity, maintaining the resistance of the heart to pathologically enhanced influences. The disorders of the cardiac rhythm which developed did so in harmony with bursts of EA of the generator, with which they were correlated in time. However, despite continuing activity of the GPEE, these disturbances were of short duration, suggesting a role of mechanisms of self-regulation of the heart in its resistance to pathological extracardial influences. This effect may perhaps be connected with changes in sensitivity of the adrenoreceptors of the heart to catecholamines during activation of the dorsal noradrenergic pathway. This suggestion is supported to some extent by data obtained in animals with adrenalin-induced myocardial damage, when neither electrical stimulation of LC nor a GPEE in it led to any visible disturbances of rhythmic activity of the heart.

These results are evidence that hyperactivation of LC may act as a factor provoking disturbances of the cardiac rhythm. At the same time, they indicate that realization of a pathological process depends not only on changes in the functional state of the control systems, but also on reactivity of the target organ. Similar relations between pathological extracardial influences and reactivity of the normal and damaged heart have been observed previously after creation of a GPEE in the amygdala, although under those conditions the rhythm disturbances were bradycardial in type [2]. The results now obtained are interesting for the study of diseases of regulation [1].

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