EFFECT OF CENTRAL GRAY MATTER LESIONS ON ANALGESIA IN RATS UNDER STRESS

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It has been shown that an endocrine system whose function is connected with inhibition of sensitivity to pain in various extremal states exists in the brain of animals. It has been suggested that one of the most important brain structures found in this system is the central gray matter (CGM), for injection of microdoses of morphine or opiate peptides into it, or electrical stimulation of this structure causes diminished sensitivity to pain [1, 3, 5, 6]. After electrolytic destruction of CGM in rats, the analgesic effect of morphine is considerably depressed [2].

The object of the present investigation was to study the effect of electrolytic destruction of CGM on the level of sensitivity to pain in rats exposed to stress.

EXPERIMENTAL METHOD

Male albino rats weighing 200-250 g were anesthetized with pentobarbital (40 mg/kg) and electrodes were inserted into CGB by a stereotaxic technique, using coordinates AP +0.6, L ± 0.5, VD +4.0 to 4.2 from the atlas [4]; an electrolytic destruction of CGM was carried out with a current of 1 mA for 25-30 sec. A mock operation was performed on rats of the control group: The electrode was inserted into brain tissue to a depth of 2.0-2.5 mm relative to the dura. The experiments were carried out 2 weeks after the operation.

A state of stress was induced by unavoidable electrical stimulation of the feet (footshock) in rats unrestrained in a chamber to the floor of which a pulsed current (2 mA, 8 pulses/min, 5 min) was applied.

Sensitivity to pain was assessed from latent periods (LP) of responseses to nociceptive stimulation. Two methods were used: the hot plate method (HPM) and the tail flick method (TFM). In the first case the rats were kept in a chamber with a floor temperature of 55°C. The time until the first time the animal licked its hind limbs corresponded to LP. The mean LP was determined from two measurements made at an interval of 15 sec. In the second case the rats were kept in a restraining box, and the tail was subjected to temperature stimulation by means of the focused beam of light from a 150-W projection lamp. LP corresponded to the time from switching on the lamp to the first movement of the rat's tail. The mean LP was obtained from 5-7 measurements at intervals of 7-20 sec.

The duration of the initial LP was determined 7-10 min before electrical stimulation, and thereafter at definite time intervals.

At the end of the experiment the animals were guillotined, the brain was fixed in 10% neutral formalin solution, and after 3-4 days sections were cut to a thickness of 60 μ on a freezing microtome. The sections were fixed on slides and photographed.

EXPERIMENTAL RESULTS

In animals after destruction of CGM, on recovery from anesthesia (after 2-4 h) periodic paroxysms of intensive motor activity were observed in the absence of visible external stimuli

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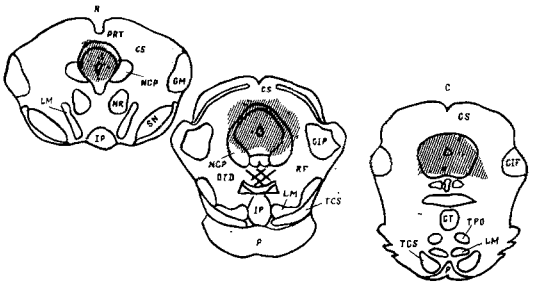

Fig. 1. The location of lesions in CGM (shaded) at different levels of rat midbrain (rostral AP + 2.0; middle AP + 10; caudal AP + 4.0). C) Caudalis, CIF) colliculus inferior, CS) colliculus superior, CT) nucl. centralis tegmenti, DTD) decussatio tegmenti dorsalis GM) corpus geniculatum mediale, IP) nucl., interpeduncularis, LM) lemniscus medialis, NCP) nucl. proprius commissural posterior NR) nucl. ruber, P) pons, PRT) area praetectalis, RF) formatio reticularis, R) rostralis, SN) substantia nigra, RF) formatio reticularis, R) rostralis, SN) substantia nigra, TCS) tractus corticospinalis, TPO) nucl. tegmenti pontis.

(light touch, shaking, unexpected photic stimuli). The motor hyperactivity was characterized by rapid rotation of the body around its longitudinal axis and movements along the walls of the cage. Uncoordinated jumps often were observed. In the intervals between paroxysms the rats were quiet. It may be assumed that these changes were connected with functional and transient disturbances of brain structures responsible for the regulation of movement coordination [2].

The results of histological investigation of the location of the lesions in CGM, illustrated in Fig. 1, show that by the method used maximal destruction of CGM was obtained in the rostro-caudal direction over a distance of 2.0-2.8 mm.

The results of a study of the duration of LP in animals of the experimental and control groups are given in Figs. 2 and 3.

It will be clear from Fig. 2 that in rats with a lesion of CGM the original LP, measured by the HPM, was significantly longer than in the control: 17.8 + 1.1 and 10.9 + 1 sec, respectively ($P < 0.002$). However, when LP was measured by the TFM (Fig. 3) no significant differences were found in its value before stimulation (4.2 + 0.4 sec in the control and 4.5 + 0.3 sec in the experiment). These results are in agreement with those published previously [2]. Differences in the values of LP measured by the HPM and TFM can evidently be explained by involvement of functionally different brain systems, regulating the state of sensitivity to pain. Under normal conditions (without application of any significant stimuli) it is probable that CGM does not play an essential role in the mechanism of the tail-flick response and the simpler response, and that it is effected either by spinal mechanisms or by systems not intimately connected with CGM. Nociceptive responses to the hot plate have a more complex reflex mechanism involving CGM and various other functionally interconnected brain structures. From this point of view the phenomenon of lengthening of the original LP, measured by the HPM in animals with a lesion of CGM, can be explained by the considerable compensatory increase in the flow of descending inhibitory influences of other analgesic systems to nociceptive spinal afferents.

The series of experiments to study the effect of CGM on the time course of the values of LP after exposure to stress revealed (Figs. 2 and 3) that immediately after the end of electrical stimulation a significant increase in LP (relative to the original values) measured by means of HPM ($P < 0.001$ for comparison of pairs) took place in the experimental and control groups. In animals of the control group the duration of LP remained significantly longer than originally for 30 min. However, in rats with destruction of CGM these values at

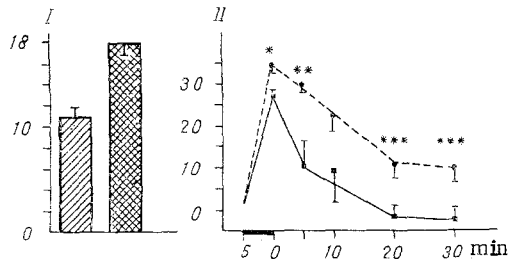

Fig. 2. Effect of destruction of CGM on duration of LP measured by the HPM before and after exposure to stress. Columns indicate duration of original LPs, obliquely shaded — original LP in rats of control group, cross-hatched — original LP in rats with lesion of CGM; broken line — time course of changes in LP in rats of control group after exposure to stress, continuous line — time course of changes in LP of rats with lesion of CGM after exposure to stress. Ordinate: I) duration of LP (in sec), II) increase in LP (in sec). *P < 0.002; **P < 0.01; ***P < 0.05.

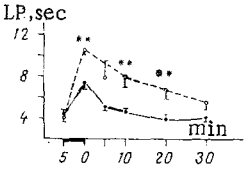

Fig. 3. Effect of destruction of CGM on time course of LP measured by TFM. Legend as to Fig. 2.

the 5th minute, although they were higher, did not differ significantly from the initial level. Similar results also were obtained during evaluation of sensitivity to pain by the TFM (Fig. 3).

Statistical analysis of the results obtained in the control and experimental groups showed that in rats with destruction of CGM the duration of responses to nociceptive stimulation (HPM and TFM) in the period after stress was significantly less than in the control animals.

It can be concluded from the results of this series of experiments that CGM participates in the functioning of analgesic systems of the brain activated by stressor stimuli. It is important to note that whereas under normal conditions destruction of CGM does not affect the duration of LP measured by the TFM, after stimulation of a stressor character the functional role of CGM becomes more important. This fact may indicate that in different states of the organism the function of the analgesic system is controlled by different mechanisms. In fact, comparison of the time course of changes in LP after stress with the time course of changes in the same parameters, but obtained previously in experiments with auricular electrical stimulation in animals with lesions of CGM shows that in the first case the duration of LP was much longer ($P < 0.001$) than in the second case. It is evident that during the action of stressor stimuli, stronger and different in modality from those associated with auricular stimulation, besides CGM, other systems such as the limbic systems are incorporated into the regulation of analgesic functions, whereas under the influence of acupuncture CGM plays a more important role.

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UNIT ACTIVITY IN THE GANGLION NODOSUM IN ACUTE CIRCULATORY AND RESPIRATORY DISTURBANCES

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The writers showed previously [3] that during stimulation of reflexogenic zones of the heart and blood vessels, neurons of the bulbar cardiovascular center responded in different ways. Discharges of some neurons, synchronized with the cardiac rhythm, changed only after stimulation of certain reflexogenic zones. Neurons whose discharges were not strictly synchronized with the cardiac rhythm varied their firing pattern in response to excitation of receptors of many reflexogenic zones. It was not clear whether activity of neurons in the cardiovascular center changes directly under the influence of the flow of afferent information from receptors of the cardiovascular system or whether it can be integrated at the level of the ganglion nodosum, on account of influences of impulses from receptors of the respiratory system on its neurons. In setting out to study this problem the starting point was the fact there is clinical and experimental evidence of close interconnection between the activities of these two systems [5]. Furthermore, in the ganglion nodosum cardial and respiratory neurons are distributed diffusely [6], and histological studies have revealed different end structures and synaptic terminals [1, 2].

EXPERIMENTAL METHOD

Experiments were carried out on 23 cats of both sexes weighing 3-4 kg. The animals were anesthetized with pentobarbital (30-40 mg/kg, intraperitoneally) and artifically ventilated on the Vita-1 apparatus, by means of which the respiration rate and the volume of inspired air can be varied. After thoracotomy bilateral vagotomy was performed above the diaphragm and the pericardium was opened; ligatures were passed beneath the pulmonary trunk and aorta at the point where they leave the ventricles, beneath the descending aorta, and beneath the circumflex branch of the left coronary artery; PVC catheters were introduced into the right and left atria. The cat was placed in a stereotaxic apparatus in the supine position. The ganglion nodosum was exposed through a parasagittal incision passing through skin, cervical fascia, and connective tissue connecting m. sternohyoideus and m. mastoideo-humeralis. The ganglion was freed from its connective-tissue capsule and placed on an insulating support. Electrical activity of the neurons was recorded extracellularly with glass microelectrodes filled with 2.5M KCl solution (resistance 7-10 MΩ). Parallel recordings were made of the pressure in the femoral artery, the ECG in standard lead II and the pneumogram, using a carbon transducer. All processes were recorded on a four-channel Medicor (Hungary) myograph. Activity of 67 neurons was analyzed by the method described in [3].

EXPERIMENTAL RESULT

Activity of three grups of neurons was studied in the ganglion nodosum: cardiovascular, with discharges synchronized with the cardiac rhythm, cardiopulmonary, whose activity coincided both with phases of respiration and with the ECG, and respiratory, whose activity was

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