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EFFECT OF CHLORPROMAZINE ON CHANGES IN CORTICAL ELECTRICAL ACTIVITY CAUSED BY *Clostridium perfringens* TYPE A TOXIN

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UDC 612.822.3.014.46:[576.851.555.097.29]-06:615.214.22

Experiments on cats showed that injection of chlorpromazine (3 mg/kg, intramuscularly) 1 h before injection of *Clostridium perfringens* type A toxin prevents the desynchronization of cortical electrical activity which usually arises in the first phase of poisoning, delays the phase of depression of electrical activity in the second phase, and increases by 50-100% the duration of survival of the animals. The effect of chlorpromazine is evidently connected with blocking of adrenergic structures of the reticular formation of the brain stem.

KEY WORDS: *electrocorticogram; toxin of* Clostridium perfringens; *chlorpromazine; reticular formation.*

Previous work showed that phasic changes in cortical electrical activity arise in poisoning caused by the toxin of *Clostridium perfringens* type A [16]. In the first phase desynchronization of electrical activity takes place, in the second it is deeply depressed. Desynchronization of cortical electrical activity was not observed after division of the midbrain (mesencephalic preparation), evidence of the role of the reticular formation (RF) in this effect. In the present investigation it was decided to study the effect of pharmacological "blocking" of the brain-stem RF on the dynamics of the EEG in this form of poisoning. A drug with such an action is chlorpromazine [2, 4, 5, 17, 20, 21].

EXPERIMENTAL METHOD

Experiments were carried out on 26 cats. Preliminary operations (tracheotomy, trephining of the skull, implantation of electrodes) were performed under local procaine anesthesia, after which pentobarbital (15-20 mg/kg) was injected intraperitoneally. The spontaneous electrocorticogram (ECoG), evoked potentials (EP) to single flashes (energy 0.3 J, distance of source of light from the cornea 40 cm), and the rhythm binding response (RBR) were recorded after 1 h. The electrocardiogram (ECG) and electromyogram (EMG) of the antigravity muscles of the neck were recorded with needle electrodes. Toxin of *Cl. perfringens* type A (100 MLD/kg body weight) and chlorpromazine (3 mg/kg body weight) were injected intramuscularly. The toxin was injected into 18 animals after EEG rhythm modification by chlorpromazine; the above indices were recorded after 6, 12, 24, 30, and 40 h.

EXPERIMENTAL RESULTS AND DISCUSSION

In cats anesthetized with pentobarbital, before injection of the toxin waves in the α and θ bands were predominant in occipital and frontal derivations; extensor tone of the anti-

Department of Microbiology and Department of Pathological Physiology, N. I. Pirogov Odessa Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR A. M. Chernukh.) Translated from Byulleten' Eksperimental'noi Biologii i Meditsiny, Vol. 84, No. 10, pp. 412-416, October, 1977. Original article submitted March 23, 1977.

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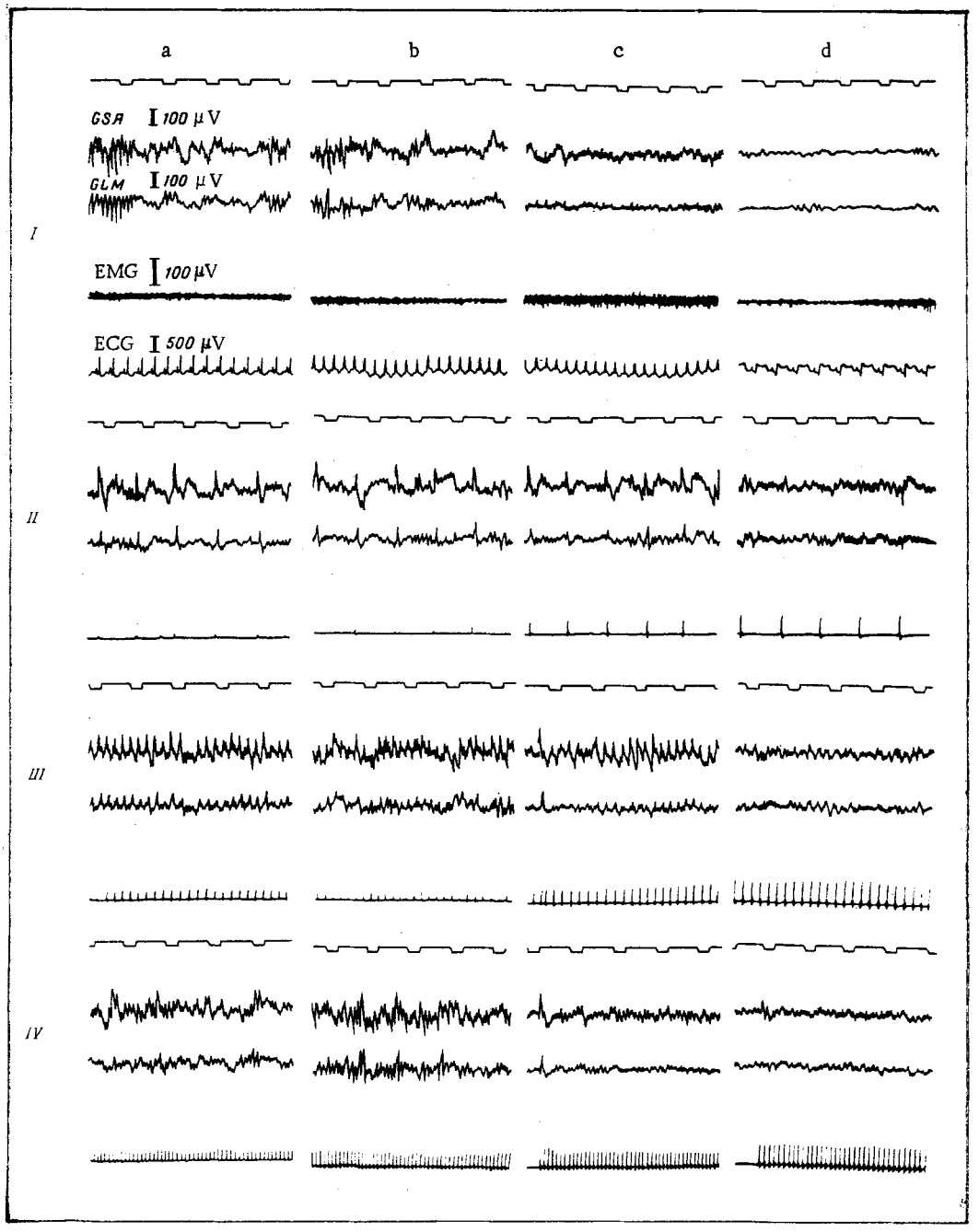

Fig. 1. ECoG, EMG, ECG, EP, and RBR during development of poisoning by toxin of *Cl. perfringens* type A in cats. a) Before injection of toxin; b,c,d) 6, 12, and 24 h respectively after injection of toxin. Here and in Fig. 2: I) (from top to bottom) time marker (1 sec), ECoG, EMG of antigravity muscles of the neck, ECG (lead II); II) EP; III and IV) RBR to regular flashes with frequencies of 5 and 10 Hz respectively. GLM) Middle part of lateral gyrus; GSA) anterior sigmoid gyrus.

gravity muscles of the neck was clearly marked, and the heartbeat was regular. Under the influence of flashes EP were generated, and regular photic stimulation caused rhythm binding in the θ and δ bands (Fig. 1).

Some decrease in the amplitude and regularity of the bursts of α-like activity was observed 6 h after injection of the toxin, the tone of the cervical muscles remained at its previous level, the T-wave on the ECG was negative, but its rhythm was regular. EP and RBR to 5 and 10 Hz were clearly defined. After 12 h desynchronization of the ECoG was observed; bursts of barbiturate α-like spindles were not recorded, and the ECoG consisted chiefly of fast low-voltage waves in the β band and α-like activity. The development of desynchroniza-

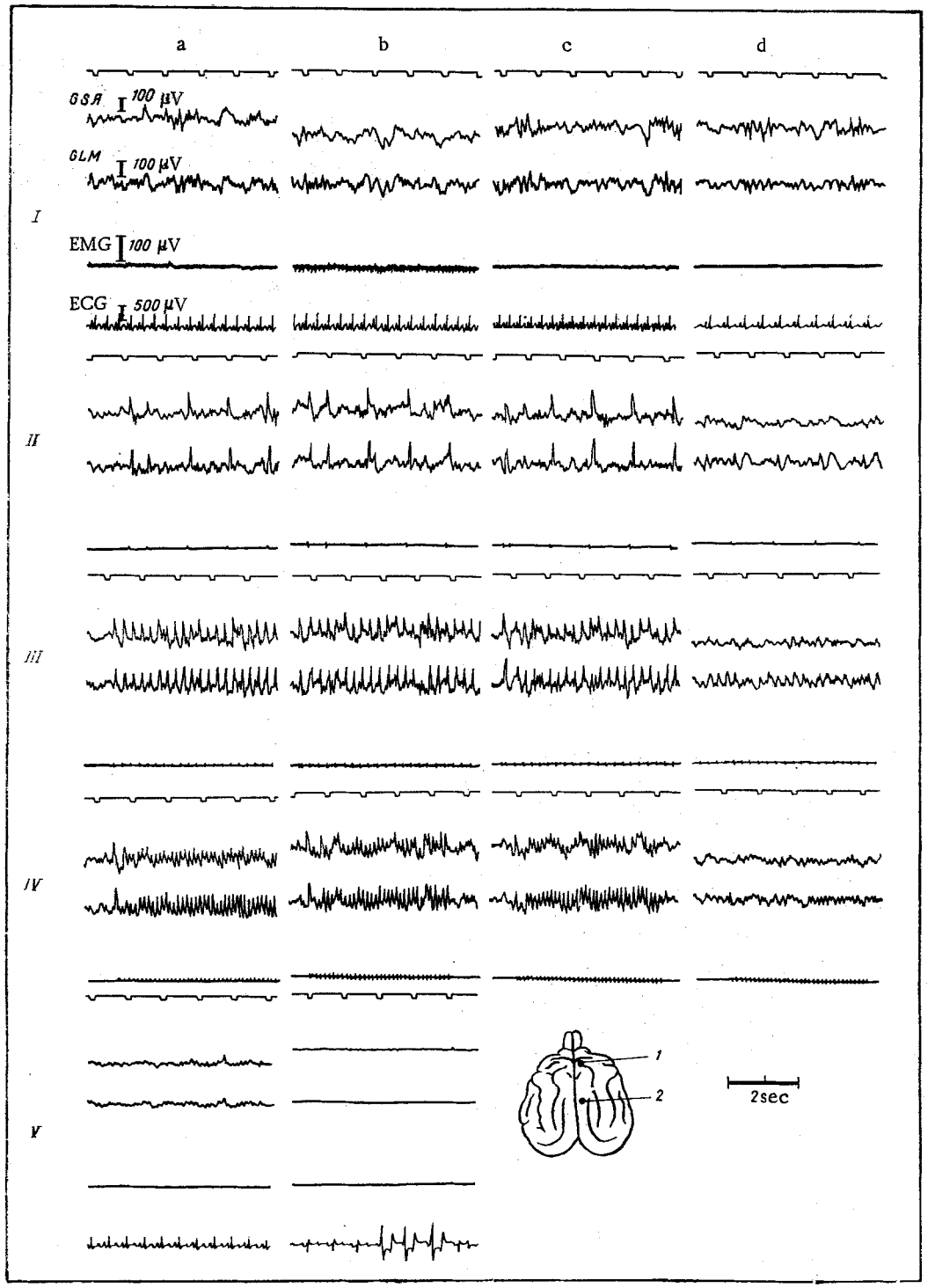

Fig. 2. ECoG, EMG, ECG, EP and RBR during development of poisoning by *Cl. perfringens* type A toxin after preliminary administration of chlorpromazine to cats. a) 1 h after injection of chlorpromazine; b,c,d,Va,Vb) 6, 12, 24, 30, and 40 h respectively after injection of toxin.

tion coincided with an increase in intensity of the EMG of the neck muscles. The heart beat as before was regular and the T-wave negative. EP to single flashes and RBR to 5 and 10 Hz were fairly well marked. After 24 h depression of ECoG was observed, no β waves were recorded, and in the frontal and occipital regions groups of α-like waves of low amplitude appeared periodically. The EMG was flattened, the T wave on the ECG was negative, and the amplitude of the R-wave varied periodically. EP to single flashes developed irregularly, their amplitude was reduced, and RBR to 5 Hz was irregular and low in amplitude, whereas to 10 Hz it was ill-defined (Fig. 1).

In the animals receiving chlorpromazine, slow waves of varied amplitude and duration in the δ band and α-like waves with a frequency of 7-9/sec appeared in the cortical electrical activity after 1 h. The antigravity muscles were in a state of moderate tonic contraction. The heartbeat was regular. In response to single flashes EP were generated in frontal and occipital leads. RBR to 5 and 10 Hz was clearly defined (Fig. 2). Bursts of spindle-like activity and slow waves in the δ band were recorded after 6 h in the frontal and occipital leads. The heart beat remained regular as before, and the neck muscles were in a state of tonic contraction. Clearly defined EP and RBR were generated in response to single regular flashes. Rhythm binding to the flashes was complete. These indices showed no appreciable change 12 h after injection of the toxin. After 24 h, waves were recorded in the δ, θ, and α bands in the spontaneous cortical activity. The tone of the antigravity muscles was sharply reduced. Against the background of a regular heart beat bradycardia and a lowering of the voltage of the P-wave were observed. In response to single flashes EP were recorded only in the occipital lead; the amplitude of the RBR waves was reduced and their duration increased. Rhythm binding to flashes with a frequency of 10 Hz was severely impaired and was incomplete. A marked weakening of the cortical activity was observed after 30 h. The EMG was completely depressed. Bradycardia remained as before and the amplitude of the P and R waves was reduced. Shortly before death of the animals (40 h after injection of the toxin) periods of almost complete bioelectrical silence in the cortex were recorded. No potentials were recorded from the neck muscles. The ECG showed sharp changes: arrhythmia and a negative T wave (Fig. 2).

After the administration of chlorpromazine there were no signs of the ECG changes characteristic of poisoning (the negative T wave and displacement of the S-T interval [9, 19], probably connected with changes in reflex excitability of brain-stem autonomic centers [15], the function of the extracardiac sympathetic nerves [10, 14], and with the direct action of the toxin on the myocardium and conducting system of the heart [14, 19]). The effect of chlorpromazine on the ECG disturbances was evidently due to its central and peripheral adrenolytic action [1, 8, 18], to weakening of pathological reflex responses from the vascular and cardiac interoceptors [11, 13], to depression of the reactivity of the hypothalamic-pituitary-adrenal system [12], and to the intensification of anabolic processes and to some decrease in the sensitivity of the tissues to hypoxia [6].

Preliminary administration of chlorpromazine also altered the character of the EEG changes under the influence of *Cl. perfringens* type A toxin. No desynchronization of the EEG was observed under these circumstances. In the late phases of poisoning a progressive decrease in amplitude of the cortical potentials developed, and cortical activity was sharply depressed. This dynamics of the EEG changes coincided with that obtained previously by the action of the toxin on mesencephalic preparations [16]. This agreement can be explained by the fact that chlorpromazine, with its high affinity for the adrenergic structures of RF, causes a distinctive type of pharmacological "blocking" of this brain-stem formation [5, 17, 18]. Special observations showed that preliminary administration of chlorpromazine considerably prolonged the life of the animals receiving the toxin.

Desynchronization of cortical electrical activity arising under the influence of *Cl. perfringens* type A toxin may be connected with the action of the toxin itself on RF and also with developing secondary pathological changes, for instance hypoxia [7]. This process is effected through involvement of the brain-stem RF, as the writers' previous experiments [16] with anatomical blocking of RF and the results of the present investigation with chlorpromazine, which blocks the adrenergic structures of RF [3, 5, 18], showed.

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