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ROLE OF THE HIPPOCAMPAL THETA RHYTHM IN THE MECHANISM OF THE ANXIOLYTIC ACTION OF PHENAZEPAM

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Previous investigations into the effect of tranquilizers on behavior of animals in a conflict situation revealed positive correlation between the intensity of their anticonflict action and their anxiolytic action in clinical practice. Correlation also was found between activity of the benzodiazepines under experimental and clinical conditions and the degree of their binding with benzodiazepine receptors [9, 11].

To determine the electrophysiological mechanisms of the anxiolytic action of benzodiazepines, in the investigation described below the effect of the benzodiazepine tranquilizer phenazepam on the functional state of various regions of the brain was studied in rats during the formation of conflict behavior.

EXPERIMENTAL METHOD

Experiments were carried out on 20 male rats weighing 180-200 g with electrodes implanted chronically into the motor cortex, dorsal hippocampus, lateral hypothalamus, and anterior thalamus. Potentials were derived by a monopolar method through implanted nichrome wire electrodes 90 μ in diameter, insulated with varnish. The reference electrode was applied to the nasal bone. Coordinates of insertion of the electrodes were calculated from an atlas of the rat brain [3]. Electrical activity was recorded on a 17-channel Nihon Kohden electroencephalograph from unrestrained animals and the traces were subsequently processed on an MAG-4V automatic integrator.

After deprivation of food and water for 48 h, inducing a motivation to drink, a stable conditioned drinking reflex was established in the rats. A conflict situation was created by collision between drinking and defensive motivation, by applying painful electric shocks to the animal while obtaining water in the customary situation of the drinking reflex [6]. Brain electrical activity was recorded on the days of training: during deprivation of drinking and 5 min after the beginning of drinking, i.e., after satiation. On the experimental days electrical activity was recorded before drinking and again 2-3 min after stimulation of the rat with electric shocks.

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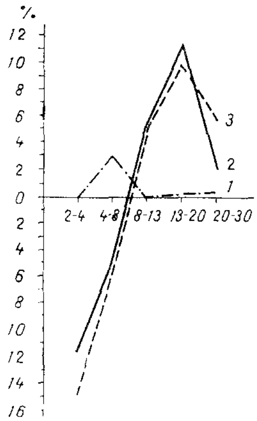

Fig. 1

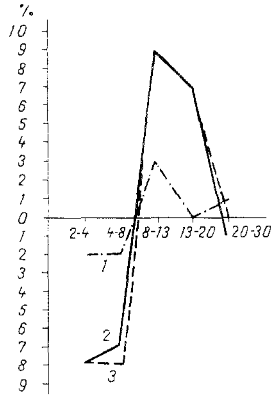

Fig. 2

Fig. 1. Relative percentage of frequencies of different spectra in EEG of dorsal hippocampus. Abscissa, frequency spectra; ordinate, ratio of frequencies to zero point, in %. Origin taken to be percentage of frequencies in the preconflict period. 1) Control after electric shock, 2) phenazepam before electric shock, 3) phenazepam after electric shock.

Fig. 2. Relative percentage of frequencies of different spectra in EEG of lateral hypothalamus. Legend as to Fig. 1.

Phenazepam was injected intraperitoneally in suspension with Tween-80, 30 min before the experiment began.

EXPERIMENTAL RESULTS

Electrophysiological analysis of the functional state of the various parts of the brain in intact rats showed that during training, the EEG recorded from the lateral hypothalamus and dorsal hippocampus of all animals during training, under conditions of water deprivation, was dominated by synchronized activity with a rhythm of 6-8 waves/sec and an amplitude of 30 to 50 μV. The EEG recorded from the motor cortex and anterior thalamus revealed an irregular rhythm with a frequency of 1.5 to 16 waves/sec, with predominance of slow waves within the 2-5 waves/sec band. After satiation of the rats with water the ECG of the lateral hypothalamus and dorsal hippocampus showed a decrease in synchronization of potentials, the rhythm became more irregular and a dominant rhythm was absent.

In the stages of initial interaction between the two opposite motivations (drinking and defensive), the animals' behavior was characterized by a very low level of motor activity, by tachycardia, and by sudden fluctuations of respiration. During this period the ECG of the lateral hypothalamus, dorsal hippocampus, and anterior thalamus revealed increased synchronization of potentials with an increase in frequency of the dominant rhythm to 8-10 waves/sec. In addition, the EEG of the motor cortex and lateral hypothalamus revealed a fall in amplitude of the waves.

Injection of phenazepam (1 mg/kg) before the beginning of the experiment caused a marked increase in low-amplitude high-frequency β-activity (13-20 Hz) in the ECG recorded from all parts of the brain, most marked in leads from the lateral hypothalamus. The frequency of the θ-rhythm varied from 7 to 8 Hz. In the initial stages of conflict formation, with the first electric shock, phenazepam abolished the animals' restraint and alertness. Under the influence of phenazepam the EEG and autonomic disturbances arising in the conflict situation were corrected. The tachycardia and extrasystoles almost completely disappeared and the percentage of animals with disturbance of respiration was reduced. The number of times the animals took water rose sharply, even though they received electric shocks. Against the background of phenazepam administration, painful electrical sitmulation caused no changes in the frequency spectrum of the EEG recorded in the various regions. The effect of the drug is demonstrated by histograms showing the relative percentage of frequencies of different EEG spectra from the hippocampus (Fig. 1) and lateral hypothalamus (Fig. 2); the relative percentage of frequencies in the preconflict period in control rats was taken as the origin.

Our experiments showed that the EEG of the dorsal hippocampus and lateral hypothalamus of rats after quenching of their thirst was marked by a decrease in synchronized activity and an increase in amplitude of the potentials, in agreement with the generally accepted view that satisfaction or inhibition of inclination is accompanied by inhibition of the hippocampal θ-rhythm.

Participation of the hippocampus and lateral hypothalamus in the regulation of motivated behavior has been demonstrated by many workers [1, 2, 4, 15]. It has been shown, in particular [2, 4], that motivated drinking and feeding behavior is formed on the basis of specific hypothalamo-hippocampal interaction. The system of structures involved in motivational excitation under these circumstances is organized according to the principle of what Anokhin [10] calls a branched functional system. Nowadays most investigators consider that the electrographic correlate of motivated behavior is the hippocampal θ-rhythm, and that its time course reflects the degree of emotional or motivational "stress" rather than its specific quality [7, 10].

The most characteristic action of the benzodiazepines is their ability to normalize animal behavior when disturbed by negative factors, which include both painful stimulation and absence of positive reinforcement [5, 12, 13]. This effect, which has been called "behavioral disinhibition," consists of strengthening of individual behavioral syndromes observed after injury to the region of the septum and hippocampus, and on that basis it has been postulated that tranquilizers affect behavior through a change in septal control of the hippocampal θ-rhythm [12, 13].

A response of aggressive-defensive type is known to correlate with a sharp increase in frequency of the dominant θ-rhythm to 8-10 waves/sec [8], but a θ-rhythm with a frequency of 7.7 Hz is recorded on the EEG in the situation of an unreinforced reflex [12, 14]. This suggests that the frequency of the dominant EEG rhythm can be used as indicator of the functional state of the brain formations studied. In the light of these data we can begin to understand the increase in the frequency of waves of synchronized activity discovered in the present investigation on EEG recorded from the lateral hypothalamus and dorsal hippocampus, immediately after the animal had taken water while receiving painful electric shocks, in a conflict situation when, after collision between two opposite motivations, the sudden painful stimulus assumes the greatest significance.

Data showing that phenazepam inhibits the hippocampal θ-rhythm in water-deprived rats, and the painful electrical stimulation under these conditions causes no appreciable changes in the frequency spectrum of the EEG, suggest that the anticonflict (anxiolytic) effect of benzodiazepines is linked with their ability to regulate the hippocampal θ-rhythm.

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