EFFECT OF DIAZEPAM ON UNIT ACTIVITY OF THE RAT SENSOMOTOR AND VISUAL CORTEX

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In acute experiments on unanesthetized, curarized rats in which cortical unit activity was recorded the threshold doses of diazepam influencing spontaneous and evoked unit activity of sensomotor and visual cortical neurons were determined. Diazepam was shown to inhibit spontaneous and evoked activity of sensomotor cortical neurons in much smaller doses than it inhibited visual cortical unit activity. It is postulated that the neurons of the anterior zones of the cortex are more sensitive to diazepam than neurons of the limbic structures and reticular formation.

KEY WORDS: *diazepam*; *cerebral cortex*; *reticular formation*.

The view is widely held that the effect of tranquilizers is connected with their influence on the limbic system [2, 7, 8, 9] and reticular formation [11]. At the same time there is evidence that tranquilizers of the benzodiazepine series have a direct action on the cerebral cortex [3, 5, 13]. Considering differences in the structure and functions of the different cortical areas, it is interesting to study the effect of tranquilizers on the electrical activity of different parts of the cortex.

In this investigation the effect of diazepam on spontaneous and evoked activity of the sensomotor and visual cortical neurons was studied.

EXPERIMENTAL METHOD

Experiments were carried out on 54 rats. Operations were performed under ether anesthesia. The rats were then fixed to a special frame, immobilized with anatruxonium (0.1-0.2 mg/kg) and artifically ventilated. Unit activity was recorded by glass microelectrodes with a tip 3-8 μ in diameter. Evoked activity arising in the sensomotor cortical neurons to stimulation of the sciatic nerve by square pulses (0.5 msec, 5 mV) from a "Multistim" stimulator and in visual cortical neurons in response to photic stimulation (pulse duration 10 msec) from a "Nihon Kohden" photostimulator was recorded. Spontaneous unit activity was recorded on magnetic tape and the results were analyzed with the "Neiron-1" statistical analyzer programmed for integrating impulses in successive time intervals (integration time quantum 2 sec, analysis time 4 min) and recorded on a "Watanabe" automatic writer. Evoked activity was recorded on photographic film from the oscilloscope screen. Diazepam was injected intravenously as a 0.1% solution, using a solvent consisting of polyethylene glycol, ethanol, and distilled water in the ratio of 3:1:6. Control experiments showed that in this concentration, injection of the solvent in a volume of not more than 0.2 ml did not affect the spontaneous and evoked unit activity in the parts of the cortex chosen for study.

EXPERIMENTAL RESULTS AND DISCUSSION

The results of the study of the effect of diazepam on spontaneous unit activity in the sensomotor cortex were as follows. In a dose of 0.25 mg/kg diazepam reduced the discharge frequency of the neurons on average by 20-30%; with an increase in the dose of the drugs to 0.5 mg/kg the depression of spontaneous activity was more marked, on average 50%.

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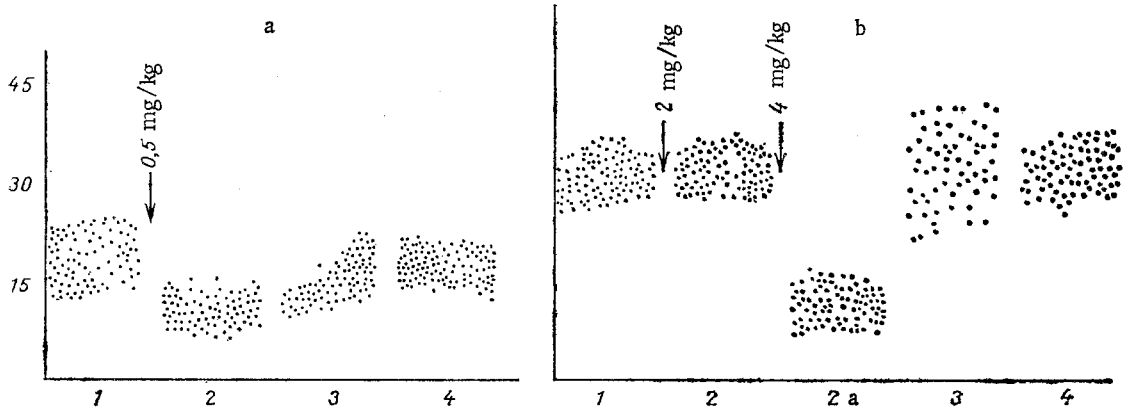

Fig. 1. Effect of diazepam on frequency of spontaneous cortical unit activity; a) sensomotor cortex; b) visual cortex. Discharge frequency: in control (1), and 15 min (2, 2a), 45 min (3), and 90 min (4) after injection of drug. Momentary discharge frequency given for histogram step of 2 sec; total duration of each histogram 4 min. Arrows indicate time of injection of diazepam.

The effect appeared 10-15 min after the injection of diazepam and its depriming action reached a maximum after 30-40 min (Fig. 1). The original background activity was restored after 70-90 min. In some experiments restoration of the original background was preceded by a phase of quickening of spontaneous activity and it was interesting to compare this with previous findings showing the existence of the phase of EEG activation at this time [5].

Diazepam also inhibited evoked activity arising in the sensomotor cortex in response to single stimulation of the sciatic nerve. A definite inhibitory action was observed after injection of diazepam in a dose of 0.5 mg/kg, and in a dose of 1 mg/kg it almost completely suppressed the evoked discharges. If diazepam was used in near-threshold doses, however, only the long-latency component of the neuronal response was inhibited and the short-latency discharge remained unchanged; it was suppressed only by the use of doses much above the threshold.

In the next series of experiments the effect of diazepam on spontaneous and evoked unit activity in the visual cortex was studied. In a dose of 2 mg/kg, in which the drug caused complete inhibition of neuronal activity in the sensomotor cortex, it had no effect on spontaneous and evoked unit activity in the visual cortex. Distinct inhibition of both types of unit activity in the visual cortex was observed after injection of diazepam in a dose of 4 mg/kg, and complete inhibition when the dose was increased to 8 mg/kg. It follows from these results that neurons of the sensomotor cortex are more sensitive to diazepam than those of the visual cortex.

It is interesting to note that the dose in which diazepam depresses hippocampal unit activity is 5-20 mg/kg. No accurate information reflecting the sensitivity of the amygdalar neurons to diazepam is available but it is known that the dose in which diazepam begins to inhibit the hippocampal-amygdalar response is 2-4 mg/kg. Meanwhile, as the results given above show, the threshold dose of diazepam for neurons of the visual cortex is 4 mg/kg, and for the sensomotor cortex 0.5 mg/kg. These results, first, confirm once again the previous suggestion that the cortex is no less sensitive to diazepam than structures of the limbic system. It also follows from these results that the anterior cortical zones are much more sensitive to benzodiazepines than all the other structures listed. Because of the considerable "overlapping" of the motor and somatosensory cortical areas in rats, the neurons of these zones were not studied separately in the present investigation. Previous experiments on cats showed [4] that diazepam depresses the late I wave of pyramidal neurons in doses in which it has no effect on the specific response in somatosensory area S-1. This suggests that in rats also the neurons of the motor cortex are more sensitive to diazepam than somatosensory neurons and that the changes in unit activity of the somatosensory cortex developing under the influence of small doses of these compounds reflect the high sensitivity of the motor part of this area to benzodiazepines. The motor cortex is known to be a zone of multisensory convergence, in which complex analysis of the flows of afferent impulses takes place, including impulses arriving from specific cortical areas, and where they are relayed

to the efferent component [10]. With this in mind, and also considering that it is in the anterior cortical zones that information from the limbic system is compared with the possibilities of efferent action, and in this way the cortical control of the emotions is brought about [6], it will be clear that the results now obtained showing the marked effect of benzodiazepine on the anterior cortical zones are of great importance for the assessment of the mechanism of action of these substances.

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EFFECT OF ETHIMIZOLE ON ENERGY METABOLISM IN THE RAT BRAIN

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In a dose of 25 mg/kg, 20 min after intraperitoneal injection, ethimizole stimulates oxidative phosphorylation, increases the creatine phosphate content and reduces the concentration of inorganic phosphorus in the brain tissue of rats. It is postulated that ethimizole stimulates energy metabolism through its activating effect on adenyl cyclase.

KEY WORDS: *high-energy compounds*; *oxidative phosphorylation*; *brain*; *ethimizole*.

A previous investigation showed that the molecular mechanism of the action of ethimizole is connected with its activating effect on adenyl cyclase [1, 3]. Ethimizole has also been shown to stimulate glycolysis in the brain [4].

In the investigation now described oxidative phosphorylation and the concentration of high-energy phosphorus compounds in brain tissue were investigated after administration of ethimizole.

EXPERIMENTAL METHOD

Male albino mice weighing 180-200 g were used. Ethimizole was injected intraperitoneally in doses of 2.5 and 25 mg/kg 20 min before sacrifice. To investigate oxidative phosphorylation the rats were decapitate., and to determine the concentrations of ATP, creatine phosphate,

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