EFFECT OF TRIFLUOPERAZINE ON TRANSMISSION OF EXCITATION IN THE RABBIT BRAIN DURING ITS PROLONGED ADMINISTRATION

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Cortical unit responses to electrical stimulation of neighboring areas were studied in experiments on waking rabbits treated with trifluoperazine in a dose of 1 mg/kg daily for 2 weeks. Measurement of dispersion of poststimulus histograms showed a decrease in the magnitude and duration of cortical unit responses after stimulation under the influence of trifluoperazine. The effect of trifluoperazine is examined from the point of view of impairment of impulse conduction in neuron nets.

KEY WORDS: *trifluoperazine; cortical neurons; brain stimulation*

Trifluoperazine has a selective antipsychotic action, directed mainly against hallucinatory, hallucinatory-delirious, and delirious syndromes [1]. The comparatively weak effect of trifluoperazine on neurons of the reticular formation [9] and its marked action on cortical neurons, the spontaneous activity of which is reorganized after prolonged administration of the drug so that the spike discharge separated by short intervals comparable in duration with the EPSPs, is reduced [6]. The conditions for temporal summation of impulses in the postsynaptic neuron are worsened [8], with the possibility of impairment of impulse conduction over the brain.

The object of this investigation was to study the action of chronic administration of trifluoperazine (as is usually adopted in clinical practice) on the function of conduction of excitation evoked by electrical stimulation of the cerebral cortex in rabbits.

EXPERIMENTAL METHOD

Waking rabbits, gently secured, were used for the experiments; trifluoperazine was injected in a dose of 1 mg/kg into the animals daily for 2 weeks. The experiments began 24 h after the last injection of the drug. Extracellular unit activity from the visual cortex of the rabbits was recorded by tungsten microelectrodes with a tip about 1 μ in diameter. Cortical electrical stimulation was carried out through bipolar macroelectrodes located 7 mm from the recording point; 10 square pulses (15 V, 100 Hz, 100 μsec) was applied.

The results were expressed as poststimulus histograms (PSHs), plotted for 10 recordings each 4 sec in duration. A temporal histogram of spontaneous activity was plotted on the same principle. For the quantitative analysis of the unit responses the dispersion of the heights of the PSH columns for spontaneous activity and responses to consecutive cuts of 1 sec was used. The values of the PSH dispersions for spontaneous activity and response were compared by calculating Fisher's criterion (F-

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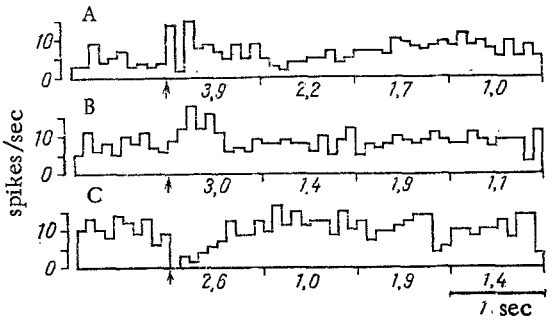

Fig. 1. Responses of three cortical neurons to electrical stimulation of neighboring cortical areas. Moment of stimulation marked by arrow. Numbers below histograms give values of F-criterion for each second after application of stimulus.

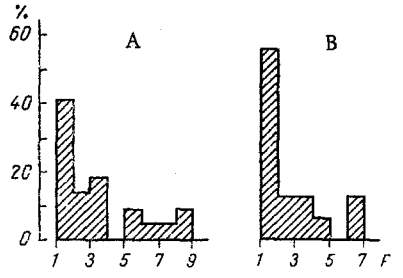

Fig. 2

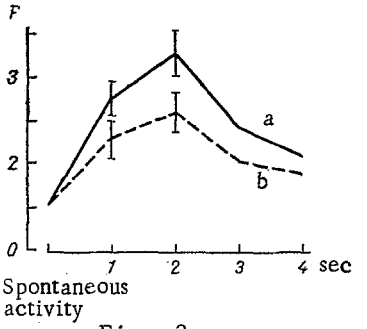

Fig. 3

Fig. 2. Distribution of values of F-criterion for single units in control (A) and after administration of trifluoperazine (B), 1 sec after electrical stimulation. Ordinate, percentage of neurons with value of F-criterion indicated on abscissa.

Fig. 3. Changes in F-criterion under the influence of electrical stimulation in control (a) and after administration of trifluoperazine (b). Abscissa, time after stimulation (in sec); ordinate, ratio of dispersions of spontaneous and response histograms (F-criterion). Vertical lines show twice the error of the means.

criterion), as a measure of the response, on the S-50 computer. In 28 experiments 23 neurons were tested under control conditions and 17 during chronic administration of trifluoperazine.

EXPERIMENTAL RESULTS

Cortical unit responses to electrical stimulation lasted for several seconds and were phasic or tonic in character (Fig. 1). Immediately after application of the stimulus some neurons developed an inhibitory pause (Fig. 1C) from 100 to 600 msec in duration, whereas others developed initial excitation which lasted not more than 100 msec (Fig. 1A). Immediately after the initial period of the response phases of activation and inhibition followed, giving the response its complex pattern that made it so difficult to describe qualitatively.

The criterion chosen for the magnitude of the response enabled a unified assessment to be made regardless of its form. This measure did not contradict the visual assessment of the response, i.e., the stronger the response, the more the spike train differed from the spontaneous pattern after electrostimulation, and the higher the value of the F-criterion.

The distribution of values of the F-criterion for single unit responses in the first second after electrical stimulation are given in Fig. 2A. In the control, 41% of neurons responded weakly to cortical stimulation ($1 < F < 2$) and 42% gave a well-marked response ($F < 3$). The mean value of the F-criterion for intact neurons was 3.5

($F < F_{0.05}$). After chronic administration of trifluoperazine, an increase in the number of neurons with a very weak response to 51% characteristically occurred (Fig. 2B) and the maximal values did not exceed 7 (9 in the control).

Trifluoperazine led to a decrease in the mean value of F to 2.6 ($F < F_{0.05}$). The dynamics of the change in the averaged F-criterion of the responses is illustrated in Fig. 3, in which the curve of the response during administration of trifluoperazine lies significantly below the control curve.

The phasic structure of the cortical unit response pattern is based on wide irradiation of the stimulus over the brain and recruiting of widely different systems and structures sending excitatory or inhibitory volleys of impulses to the test neuron, into the response. Their simultaneous or successive arrival at the neuron creates the complex phasic rearrangement of the discharge.

Analysis of the phasic variation of cortical unit responses showed that after chronic administration of trifluoperazine, as usually used for the treatment of patients with psychoses, this variation was reduced but the duration of the total response was shortened. This could perhaps indicate that excitation arising in the CNS is more localized during the action of the neuroleptic and is extinguished faster.

This process could be due to various causes: a change in the excitability of the nerve cells, lowering of the function of the nerve fibers and, finally, inhibition of synaptic transmission. Among the factors listed above it is easiest of all to rule out a contribution of the conduction system of the central neurons, for neuroleptics are known to be localized selectively in the gray matter [10]. Meanwhile, considerable changes in the body of the neurons and synapses following administration of a single dose and, in particular, chronic administration of trifluoperazine [4], have been demonstrated histologically [7], histochemically [2], and electron-microscopically.

The mechanism of synaptic transmission of the nervous impulse is most sensitive to neuroleptics. This has been shown for the neuromuscular junction [5] and in several regions of the CNS [3]. As a result of the decrease in effectiveness of the synaptic "bombardment," conduction of the nervous impulse along the structures of the neuron is worsened, and this is expressed as a decrease in the amplitude of the unit response to cortical stimulation.

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