CHANGES IN THE STRUCTURE OF SPIKE TRAINS OF CORTICAL NEURONS PRODUCED BY PROLONGED ADMINISTRATION OF DIFFERENT DOSES OF NEUROLEPTICS

A. V. Nemtsov and A. I. Kurochkina

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Experiments on waking rabbits with recording extracellular cortical unit activity showed that administration of chlorpromazine and trifluperazine in doses of 1 and 5 mg/kg for 2 weeks led to an increase in the mode of distribution of interspike intervals on account of a decrease of the short (not more than 40 msec) intervals in the unit discharges. This effect of the neuroleptics was stable for it was observed 24 h after the end of the course of injections; it depends on the dose of the preparations and was stronger with trifluperazine than with chlorpromazine.

A previous investigation showed that prolonged injections of chlorpromazine and trifluperazine to rabbits in doses of 1 mg/kg, by contrast with a single injection of the same dose of the compounds, causes a shift in the maximum (mode) of distribution of interspike intervals into the region of higher values [2]. It was also shown that inhibition of unit responses to external stimulation is connected with this property of the neuroleptics.

A quantitative analysis was accordingly made of certain neuronal effects produced by different doses of chlorpromazine and trifluperazine during prolonged administration.

EXPERIMENTAL METHOD

Experiments were carried out on lightly secured waking rabbits in which unit activity of the visual cortical neurons was recorded extracellularly with tungsten microelectrodes. The compounds were injected intramuscularly in doses of 1 or 5 mg/kg daily for 2 weeks. Tests were carried out 24 h after the end of course of injections. The action of the compounds was assessed by comparing the mean firing rate of the neurons and the distribution of ISI with a step of 10 msec in the intact animals and in animals after receiving chlorpromazine and trifluperazine. Altogether 182 neurons with stable spike trains were chosen for analysis. Stability was determined by distributions of ISI from consecutive parts of the record of unit activity [4]. Characteristics of the distributions of the ISI were obtained and their statistical analysis carried out with the M-220 computer.

EXPERIMENTAL RESULTS AND DISCUSSION

The mean spontaneous firing rate of the cortical neurons proved to be an uninformative parameter for the investigation of prolonged administration of neuroleptics, for doses of 1 and 5 mg/kg daily did not cause any statistically significant changes in this parameter.

More definite differences as regards the compounds themselves and their doses were obtained by analysis of the structure of the spike trains of the neurons recorded as the distribution of ISI. Histograms of modal values of these distributions are given in Fig. 1. Half of the neurons in the intact animals had

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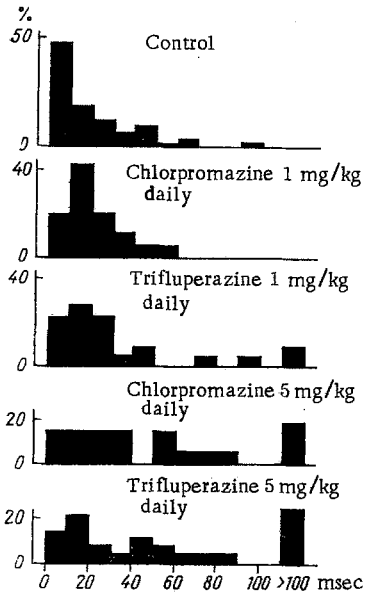

Fig. 1

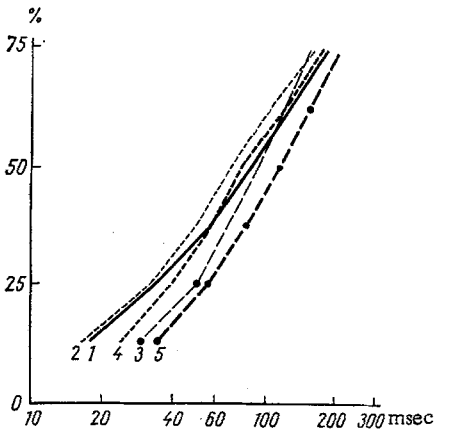

Fig. 2

Fig. 1. Histograms of modes of distributions of ISI of cortical neurons in five series of experiments. Ordinate – percentage of neurons for which distribution of ISI has the mode indicated on the abscissa.

Fig. 2. Mean values of characteristics of distributions in control and after prolonged administration of neuroleptics. Abscissa – mean values of octiles (in msec; logarithmic scale); ordinate – value of percentage points of distribution (octiles). 1) Control; 2) chlorpromazine 1 mg/kg; 3) chlorpromazine 5 mg/kg; 4) trifluperazine 1 mg/kg; 5) trifluperazine 5 mg/kg. Filled circles represent octiles differing from control at a level not below 95%.

a mode of not more than 10 msec. Under the influence of chlorpromazine and trifluperazine in a dose of 1 mg/kg daily the predominant neurons were those with distributions of ISI with a mode in the region of 11-20 msec ($P<0.01$). The greatest shift was produced by trifluperazine. Meanwhile, after prolonged administration of trifluperazine, neurons for which the distribution of ISI had as its maximum a plateau in the region of 100 msec began to appear (Fig. 1).

With an increase in the dose of the neuroleptics to 5 mg/kg daily there was a further shift of the mode of distributions of the ISI. With this dose the distributions for the neurons also became plateau-shaped after administration of chlorpromazine (Fig. 1). By this parameter trifluperazine was the more active drug in a dose of 5 mg/kg also, although the differences between the two drugs in this case were rather less marked.

Analysis of the maxima of the distributions of ISI thus showed that the action of the neuroleptics is to shift the modal values of the ISI; with respect to this effect the compounds and their doses can be arranged in the following order: chlorpromazine 1 mg/kg <trifluperazine 1 mg/kg <chlorpromazine 5 mg/kg <trifluperazine 5 mg/kg.

The question arises: What changes in the spike train of the cortical neurons took place in order to displace the mode of the ISI distributions? To answer this question the octiles (successive part of 12.5%) of the distributions of all 182 neurons were calculated. The averaged results of the calculations are given in Fig. 2. Under the influence of the neuroleptics there was a relative decrease in the spike train of the cortical ISI. The exception was chlorpromazine in a dose of 1 mg/kg daily, and the shift of the mode of distributions in this series of experiments (Fig. 1) was evidently due to a relative increase in the number of intervals of 20-70 msec in the spike train (Fig. 2). After administration of trifluperazine in the same dose there was a decrease in the number of ISI under 24 msec in duration. Even more substantial changes in the short intervals were produced by chlorpromazine and trifluperazine in doses of 5 mg/kg daily. The range of changes was widened to 29 and 34 msec, respectively.

The action of the neuroleptics was thus to change the spike trains of the cortical neurons by reducing the number of the shortest ISI, comparable in duration with the EPSP [3]. The decrease in the number of these intervals in the spike train must reduce the probability of summation of the separate EPSPs and must thus impair the ability of the neurons to conduct impulses. This phenomenon evidently lies at the basis of inhibition of summation responses in the CNS by neuroleptics [1], and it can be explained by the well-marked membranotropic action of these drugs [5].

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