ment of an anxiety-relieving effect. Aminoacetic acid, which raises the GABA level in the brain by 200%, or muscimol does not induce a selective tranquilizing effect [1, 7]. As the observations described above show, substances of the n-DPA type, which behave mainly as regulators of the GABA system, and which differ in the mechanism of their action from benzodiazepines, may have a more adequate influence on emotional and behavioral processes.

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THE ACTIVATING EFFECT OF SMALL DOSES OF HALOPERIDOL

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UDC 615.214.22:547.829].015.4

KEY WORDS: haloperidol; small doses; activating effect; inhibition.

In recent years many investigators have directed their efforts toward the study of the mechanisms of action of neuroleptics of the butyrophenone series and, in particular, of haloperidol. This drug is widely used in the treatment of schizophrenia and it differs from other neuroleptics in the fact that its antipsychotic action is not accompanied by any marked depriming effect. It has been shown that haloperidol can exert a tranquilizing action, which has been found both clinically [11] and experimentally [9], and in this respect it exhibits similarity with tranquilizers of the benzodiazepine series. Since we know that the benzodiazepine tranquilizers, if administered in small doses, are characterized by an activating action, exhibited as facilitation of impulse summation in the nervous system [5] or as increased motor activity [3] and EEG desynchronization [6], it is interesting to examine whether haloperidol, in small doses, also possesses such an activating effect.

The object of this investigation was to study the effects of small doses of haloperidol by the use of screening tests and electrophysiological indices.

EXPERIMENTAL RESULTS

The effect of haloperidol in doses of 0.05-0.15 mg/kg on the motor activity of rats and mice (in groups of five animals at a time) was investigated by means of an Animex actometer (LKB, Sweden). The animals'

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(Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 91, No. 1, pp. 48-50, January, 1981. Original article submitted June 20, 1980.

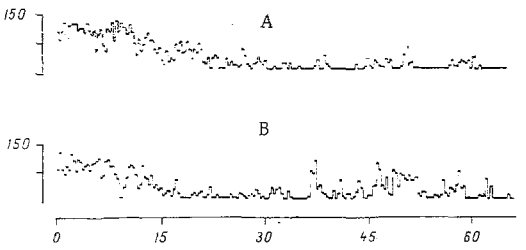

Fig. 1

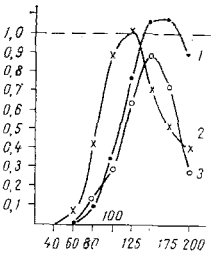

Fig. 2

Fig. 1. Changes in motor activity of albino rats under the influence of haloperidol 0.15 mg/kg. Motor activity of two groups, each consisting of five animals. A) Control, B) effect of haloperidol. Abscissa, time (in min); ordinate, number of movements per minute.

Fig. 2. Effect of haloperidol on recovery cycles of primary response of rat sensomotor cortex. 1) Before, 2) 35 min and 3) 120 min after intraperitoneal injection of 0.15 mg/kg haloperidol. Abscissa, intervals between conditioning and testing stimuli (in msec); ordinate, ratio of amplitudes of testing and conditioning responses. Difference between curves 1 and 2 is significant ($P < 0.05$).

movements, transformed into standard electrical pulses, were led from the output of the Animex instrument to the input of an LP-4840 multichannel analyzer (Nokia, Finland); in the course of the investigation motor activity was counted and its parameters (mean, duration of the different phases) were determined. The results of analysis were recorded as graphs by an automatic writer; the significance of differences between motor activity in the control and under the influence of haloperidol was determined by the nonparametric criterion of signs [4]. Interaction between haloperidol and bicuculline was studied on albino mice weighing 18-22 g. Convulsions induced by bicuculline were used as the model of the GABA-negative action. Haloperidol was injected intraperitoneally in a dose of 0.05 mg/kg and bicuculline was injected subcutaneously in a dose of 2-3.5 mg/kg, 30 min after the haloperidol. The value of ED_{50} of the convulsant, i.e., the dose in which it induces convulsions with a total abundance of 50% of maximal (20 of 40 possible points during 4-point rating, with 10 mice in the group) was calculated [12]. Cycles of recovery of the primary response of the sensomotor cortex in 22 rats were used as electrophysiological indices of the change in excitability of the brain. To record them the sciatic nerve was stimulated by paired pulses of constant voltage (amplitude 1-2 V, duration 300 μsec), the intervals between which varied from 20 to 300 msec. Evoked potentials recorded in the focus of maximal activity of the primary response of the sensomotor cortex were averaged by means of the LP-4840 multichannel analyzer (Nokia, Finland), after which the amplitudes of responses to both stimuli were measured and the ratio of the amplitude of the second or test response to the amplitude of the first or conditioning response was calculated for each interval between stimuli. Parallel with evoked potentials, electrocorticograms of the sensomotor cortex were recorded.

EXPERIMENTAL RESULTS

Animals of the control group (Fig. 1A), which received an intraperitoneal injection of 0.2 ml physiological saline, when placed in the chamber of the Animex apparatus, exhibited investigative activity for 15-25 min. This activity then declined and the animals formed a group, i.e., their aggregation was observed [8]. Haloperidol in doses of 0.5-2 mg/kg had a depriming action on motor activity, but in doses of 0.05-0.15 mg/kg it caused activation: 34 min after injection (Fig. 1B) motor activity was intensified for about 20 min (difference from the control significant; $P < 0.05$).

It was also shown that by contrast with average doses (0.5-1 mg/kg), which have a protective action against convulsions induced by bicuculline [7], in small doses (0.05-0.15 mg/kg) haloperidol potentiated its convulsant action. This was shown by a tendency (not significant) for ED_{50} of bicuculline to be reduced, from 3 (2.51-3.57) mg/kg in the control to 2.32 (1.95-2.76) mg/kg after injection of haloperidol.

The activating effect of haloperidol also was demonstrated by the electrophysiological indices. The recovery cycle of the primary response of the rat sensomotor cortex was marked by a phase of depression of the testing response with intervals of 20-100 msec between stimuli and by a phase of its facilitation with intervals of 125-300 msec (Fig. 2). The phase of depression of the testing response in recovery cycles of evoked

potentials corresponded to inhibition of neuronal activity [10-13], which reflects the activity of active inhibitory mechanisms in the cerebral hemispheres. Haloperidol (0.15 mg/kg) 30-35 min after injection weakened inhibition in the cerebral cortex, as revealed by a decrease in depression of the testing response with intervals of 20-100 msec between stimuli (Fig. 2). These changes in cortical excitability were accompanied by desynchronization of the EEG. Recovery of the original recovery cycles of the primary response (Fig. 2) and of the EEG was observed 100-120 min after injection of haloperidol.

Unlike in large and average doses, in small doses haloperidol thus has an activating action. This is manifested as increased motor activity and enhancement of the convulsant effect of bicuculline, and it is evidently the result of weakening of GABA-ergic inhibitory processes in the brain. Depending on dose, haloperidol thus has different actions: In doses of over 1 mg/kg it does not affect GABA-ergic processes, in average doses (0.3-0.5 mg/kg), for which a tranquilizing effect is described [8], it has a GABA-mimetic action [7], but in small doses (0.05-0.15 mg/kg) it has an activating and, evidently, GABA-negative action.

Consequently, the similarity observed previously between haloperidol and the benzodiazepine tranquilizers extends also to small doses of these drugs. It is important to note that this similarity is manifested under both experimental and clinical conditions, for both haloperidol [1] and diazepam [2] have been shown to have an activating action clinically. The similarity between the pharmacological properties of these drugs suggests that they share common mechanisms of action.

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