Depression of the function of the baroreceptor reflexes in repeated emotional-stress states is one mechanism of development of chronic hypertensive states [1]. Activation of the diencephalic mechanisms, in connection with the development of emotional stress, weakens the antihypertensive action of the baroreceptor reflex mechanisms [8, 9]. Accordingly, improvement of the central baroreceptor reflex regulation accompanied by a simultaneous decrease in the pressor reflex and tachycardia due to emotional stress, is a valuable manifestation of the autonomic effect of hydiphen which must be taken into account when it is used clinically.

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ROLE OF GABA-ERGIC STRUCTURES IN THE MECHANISM OF ACTION OF HALOPERIDOL

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The effect of haloperidol on convulsions induced in mice by bicuculline and thiosemicarbazide and on recovery cycles of the primary sensomotor cortical response in rats was studied. In a dose of 0.3-0.5 mg/kg, giving a tranquilizing effect, haloperidol had a protective action against convulsions induced by blockade of GABA receptors through the action of bicuculline, and potentiated depression of the testing response in the recovery cycle of the primary sensomotor cortical response in rats, i.e., within this dose range haloperidol potentiates GABA effects. With an increase in the dose of haloperidol to 1-2 mg/kg its effectiveness in both tests disappeared. On the basis of these results and data in the literature it is suggested that the postsynaptic GABA-positive effect plays an important role in the mechanism of the tranquilizing action of haloperidol and of other neurotropic agents.

KEY WORDS: haloperidol; tranquilizing effect; GABA.

The presence of a linear group between the rings in the structure of aminobutyrophenones, similar in its structure and spatial distribution of charges to the molecular of γ-aminobutyric acid (GABA) [9, 11], was the basis for the assertion that these substances can simulate the effects of GABA [14]. However, butyrophenones, including their most typical representative, haloperidol, have not hitherto been investigated on models of GABA-ergic effects, which could confirm or refute this suggestion. The only investigation to provide convincing evidence of the GABA-positive action of another representative of the butyrophe-

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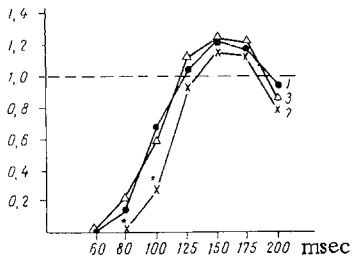

Fig. 1. Effect of haloperidol on recovery cycles of primary sensomotor cortical response in rats. Abscissa, interval between stimuli (in msec); ordinate, ratios of amplitudes of testing and conditioning responses. Horizontal broken line indicates equality of the two responses. 1) Control; 2) 30 min after injection of haloperidol (0.4 mg/kg, intraperitoneally); 3) 90 min after injection of haloperidol; *) $P<0.05$.

nones, namely droperidol, is described in [13], but nevertheless the fact that the authors cited used only microiontophoretic application of droperidol makes it difficult to compare the effects observed with the action of known doses of the drug administered systemically.

The object of the present investigation was to study the effect of different doses of haloperidol by a method of specific neuropharmacological screening based on detection of its relations with GABA-ergic agents and on electrophysiological analysis of the intensity of GABA-ergic inhibitory processes.

EXPERIMENTAL METHOD

Interaction of haloperidol with GABA-ergic substances was studied in experiments on albino mice weighing 18-22 g. Convulsions induced by bicuculline and thiosemicarbazide were used as models of GABA-negative effects. Haloperidol was injected intraperitoneally in doses of 0.3-0.5 and 1-2 mg/kg. Bicuculline was injected subcutaneously in a dose of 1.5-3.5 mg/kg 30 min after injection of haloperidol; thiosemicarbazide also was injected subcutaneously in a dose of 12-18 mg/kg, 15 min before haloperidol (counting the times of maximal activity of thiosemicarbazide to be 50-70 min). ED_{50} of the analeptic [the dose in which it causes convulsions with a total intensity of 50% of maximal: 20 points (of a possible 40) on a four-point scale, 10 mice in the group] and LD_{50} (the 50% lethal dose) were calculated by the method in [12].

As an indicator of the intensity of inhibitory GABA-ergic processes the recovery cycle of the primary response was investigated. Experiments were carried out on 32 unanesthetized immobilized male albino rats weighing 200-250 g, with operations performed under ether anesthesia. The sciatic nerve was stimulated by pairs of pulses with intervals of 40-300 msec, with a frequency of 1 Hz, duration 0.3 msec, and amplitude 1-2 V (the stimulus intensity was 30% over threshold). Potentials were recorded at the focus of maximal activity of the primary sensomotor cortical response and, after amplification, they were led to the input of a Nokia LP-4840 multichannel analyzer for averaging in the course of the experiment; the results of presentation of 50 pairs of stimuli were averaged.

EXPERIMENTAL RESULTS AND DISCUSSION

Haloperidol in a dose of 0.3-0.5 mg/kg gave a distinct protective effect against convulsions induced by bicuculline. Both a decrease in the intensity of clonic convulsions and a decrease in the number of deaths were observed. ED_{50} for bicuculline, for instance, was increased from 1.72 (1.5-1.96) mg/kg in the control to 2.4 (2.09-2.76) mg/kg after preliminary injection of 0.3 mg/kg haloperidol.

TABLE 1. Comparison of Results of Neuropharmacological Study of Neuroleptics of the Butyrophenone and Phenothiazine Series and of Benzodiazepine Tranquilizers (Nos. 1-3) with Certain Neurochemical Characteristics (Nos. 4-6)

Effect	Haloperidol		Chloropromazine	Diazepam
	tranquilizing dose	neuroleptic dose		
1. Antagonism with bicuculline	+	—	—	+(3,4)
2. Potentiation of GABA-ergic inhibi.*	+	—	—	+(3,4)
3. Antagonism with thiosemicarbazide*	—	—	—	+(3,4)
4. Increase in sensitivity of postsynaptic receptors to GABA †	± (Droperidol 13)		— (13)	+ (2)
5. Depression of reassimilation of GABA‡	+ (5,10)		+ (5,10)	± (10)
6. Inhibitation of enzymic inactivation of GABA	0	— (7)*	— (15)‡	+ (1,3)*

Legend. 1. *) Data obtained *in vivo*, †) results of experiments with microontophoretic application of drugs, ‡) results of experiments *in vitro* published in the literature. 2. +) Effect present, —) effect absent, ±) weak effect; 0) no personal or published data available; numbers in parentheses correspond to literature cited.

LD_{50} for bicuculline was increased from 2.7 (2.37±3.07) in the control to 3.6 (3.16-4.11) when administered after haloperidol. The analeptic effect of thiosemicarbazide was unchanged by haloperidol.

In a dose of 0.3-0.5 mg/kg haloperidol potentiated depression of the testing potential in the recovery cycle of the primary sensomotor cortical response of rats in the interval of 60-100 msec between stimuli (Fig. 1). Since the writers showed previously that this phase of the recovery cycle (close in its duration and dynamics to the IPSP) is selectively modified by the action of GABA-ergic substances [4], it can be tentatively suggested that the drug, in these doses, potentiates GABA-ergic inhibition in the cerebral cortex.

After injection of haloperidol in a dose of 1-2 mg/kg the intensity of the analeptic effect of bicuculline and the frequency of death were unchanged. Electrophysiological study of these doses of the neuroleptics showed that it changed the intensity of depression of the testing response within the interval of 60-100 msec characteristic of GABA-ergic effects. In these experiments, the character of the effects of the doses of haloperidol used was shown to differ in principle. The characteristics of these effects and a comparison of the data now obtained with those in the literature for phenothiazine neuroleptics and benzodiazepine tranquilizers are given in Table 1. They show that, in agreement with suggestions expressed previously, haloperidol in fact has a GABA-positive action, but gives this effect only over a narrow dose range (0.3-0.5 mg/kg), within which, according to data in the literature, its characteristic effect is tranquilizing and not neuroleptic [6]. In these doses the action of haloperidol shows definite similarity with that of tranquilizers of the benzodiazepine series, which have been shown to be capable of potentiating GABA effects in various brain structures [3, 8].

However, this similarity is incomplete: In the above doses haloperidol has a protective effect only against bicuculline convulsions which, as we know, are due to blockade of postsyn-

aptic GABA receptors, whereas tranquilizers of the benzodiazepine series are active against convulsions induced not only by bicuculline, but also by thiosemicarbazide, which retards GABA formation. Whereas tranquilizers of the benzodiazepine series have a GABA-positive action both as a result of an increase in the sensitivity of GABA-ergic receptors [2] and because of slowing of enzymic inactivation of the mediator [1, 3], the GABA-positive action of haloperidol, it can tentatively be suggested, is due to a GABA-mimetic effect, attributable to the structural similarity of part of the haloperidol molecule with the GABA molecule.

Large doses of haloperidol, giving a neuroleptic effect, exhibit no features of a GABA-positive action. The reason for this may be the experimentally discovered [7] ability of haloperidol to inhibit glutamate dehydrogenase activity and, as a result, to lower the glutamate and GABA concentrations in brain tissue. The fall in GABA concentration, which reaches 28% after injection of 1 mg/kg of haloperidol, can evidently neutralize its GABA-mimetic action.

Haloperidol, like chlorpromazine, is known to be an active inhibitor of GABA assimilation [5, 10]. However, benzodiazepines, which reduce the rate of GABA assimilation very slightly [10], sharply increase the intensity of GABA-ergic postsynaptic inhibition [2, 4]. Taken together, these factors are evidence primarily of the chemical heterogeneity of structures responsible for the reaction of GABA with postsynaptic receptors and for its interaction with the reassimilation system. Data on the GABA-positive effect of tranquilizing doses of haloperidol, in conjunction with evidence of the GABA-sensitizing effect of tranquilizers of the benzodiazepine series suggest an important role for the postsynaptic GABA-positive effect in the realization of the tranquilizing action of neurotropic drugs.

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