EFFECT OF TRIFLUOPERAZINE AND HALOPERIDOL ON ACTIVITY OF PHENAZEPAM

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In recent years tranquilizers of the benzodiazepine series and, in particular, the first Soviet drug of this class, phenazepam [1], have found ever-wider application in hospital and out-patient practice. However, in some forms of diseases phenazepam does not have the desired therapeutic action. In such cases a combination of phenazepam with drugs of other groups, such as neuroleptics, may be tried. For instance, in the treatment of some forms of neurosis phenazepam is given in combination with trifluoperazine, and in the treatment of some cases of schizophrenia it is given in combination with haloperidol and lithium salts [1, 5]. A combination of phenazepam with neuroleptics of different chemical structure has enabled the field of its application to be widened. The mechanism of action of these drugs, however, in such cases is not sufficiently clear.

The aim of this investigation was to study the anticonvulsant activity of phenazepam in combination with trifluoperazine or haloperidol, in mice with seizures induced by metrazol. This test is one of the most informative for predicting the anxiolytic action of tranquilizers [3]. Since tranquilizers of the benzodiazepine series are known to potentiate GABA-ergic inhibition in the cerebral cortex [6] another aim of this investigation was to study the action of the above-mentioned combinations of drugs on recovery cycles of primary responses of the sensomotor cortex in rats, which adequately reflect the state of cortical inhibitory systems.

EXPERIMENTAL METHOD

Changes in the convulsant action of metrazol under the influence of phenazepam and its combination with neuroleptics were studied in 240 noninbred male albino mice weighing 18-22 g. The number of deaths and the convulsant effect were determined in groups (10 animals in each group) and recorded on a four-point system (+ twitching of the limbs, ++ clonic convulsions, +++ clonico-tonic convulsions, ++++ tonic extension terminating in death). The value of ED_{50} for phenazepam and its changes when administered together with neuroleptics were than calculated. The comparative anticonvulsant activity of phenazepam separately and in combination was determined from ED_{50} values [2]. Trifluoperazine and haloperidol were injected intraperitoneally 45 min, and phenazepam 15 min before injection of a standard dose of 110 mg/kg of metrazol [4].

Electrophysiological investigations were carried out on 28 noninbred male albino rats weighing 180-250 g. To obtain recovery cycles or the primary sensomotor cortical response, the sciatic nerve was stimulated through bipolar nichrome electrodes with paired pulses of constant voltage, 0.3 msec and with an amplitude of 1-2 V produced by an ESU-1 stimulator. Intervals between pulses varied from 80 to 200 msec. Potentials were derived in the focus of maximal activity of the primary response. After amplification the evoked potentials were averaged in the course of the experiments by means of a "Nokia" LP 4840 (Finland) multichannel analyzer. The amplitude of the responses to both stimuli of the pair was then measured and the ratio of the amplitude of the second (testing) to that of the first (conditioning) responses was calculated for each interstimulus interval. Details of the method were described previously [7].

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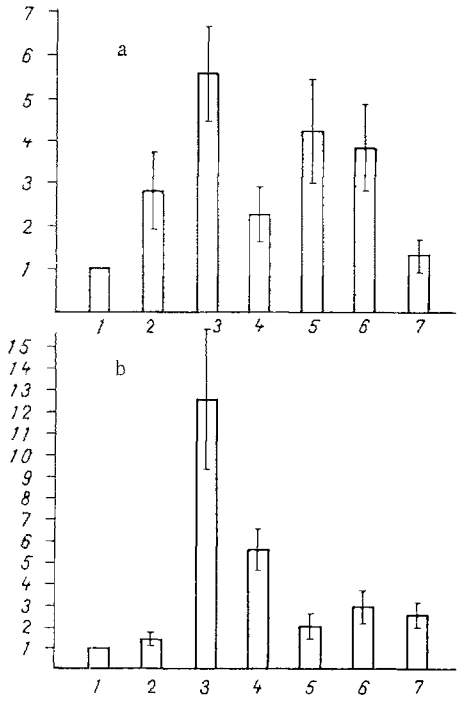

Fig. 1. Comparison of relative anticonvulsant activity of phenazepam and its combinations with haloperidol and trifluoperazine (activity of phenazepam taken as 1). a) Convulsant effect assessed in points, b) convulsant effect assessed as per cent mortality. 1) Phenazepam; 2, 3, 4) combinations with haloperidol in doses of 0.5, 0.1, and 0.05 mg/kg respectively; 5, 6, 7) combination with trifluoperazine in dose of 0.5, 0.1, and 0.05 mg/kg respectively. Ordinate, relative anticonvulsant activity (in conventional units).

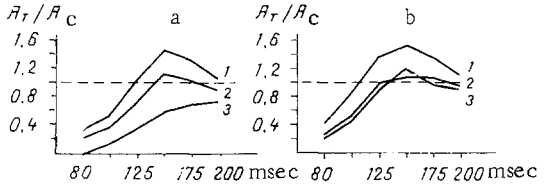

Fig. 2. Potentiation of depriming effect of phenazepam on recovery cycles of primary sensomotor cortical response of rats under the influence of haloperidol (a) and its absence after administration of trifluoperazine (b). a: 1) Control, 2) 25 min after injection of phenazepam (0.15 mg/kg), 3) 40 min after injection of trifluoperazine (0.5 mg/kg) and 65 min after injection of phenazepam. Abscissa, intervals between stimuli (in msec); ordinate, ratio between amplitudes of testing and conditioning responses. Broken horizontal line denotes equality of amplitudes of two responses.

EXPERIMENTAL RESULTS

Experiments on mice showed that haloperidol potentiates the protective action of phenazepam against seizures induced by metrazol. This was manifested as a considerable (five-sixfold) reduction in ED_{50} of phenazepam (to 0.15 mg/kg) compared with that for its administration without neuroleptics. The anticonvulsant activity of the combination of drugs increased with an increase in the dose of haloperidol from 0.05 to 0.1 mg/kg (under these circumstances ED_{50} of phenazepam fell from 0.065 to 0.027 mg/kg), but with an increase in the dose of the neuroleptic to 0.5 mg/kg, the anticonvulsant activity fell (ED_{50} of phenazepam, 0.054 mg/kg; Fig. 1). Haloperidol, incidentally, potentiated the effect of phenazepam in a dose (0.1 mg/kg) much less than that in which phenazepam itself has a tranquilizing action

(0.4-0.6 mg/kg) [8]. During combined administration of phenazepam with trifluoperazine, potentiation of the anticonvulsant activity also was observed. This effect increased with an increase in the dose of trifluoperazine and was maximal in a dose of 0.5 mg/kg (Fig. 1). ED_{50} of phenazepam in such a combination was 0.035 mg/kg. However, unlike haloperidol, trifluoperazine potentiated the anticonvulsant action of phenazepam most distinctly in doses approximately equal to that in which phenazepam itself has a tranquilizing action [8].

The results of the electrophysiological investigation showed that haloperidol in a dose of 0.1-0.2 mg/kg potentiates both depression of the testing response in recovery cycles of the primary sensomotor cortical response of the rats and also synchronization of the EEG induced by phenazepam (Fig. 2). The effect of haloperidol was maximal 30-40 min, and it disappeared 90-120 min after injection. Unlike haloperidol, trifluoperazine in the same doses as those mentioned in the first part of the work, potentiated the synchronizing action of phenazepam on the EEG but caused no change in its effect on recovery cycles of the primary somatosensory cortical response (Fig. 2). An increase in the dose of the two drugs did not lead to depression of the testing response.

Under the influence of neuroleptics the protective action of phenazepam against metrazol-induced seizures was thus strengthened; synergism with haloperidol, moreover, was more marked than with trifluoperazine. Probably the greater effectiveness of a combination of phenazepam with haloperidol was due to a certain similarity between the mechanisms of action of benzodiazepine and haloperidol, but the absence of any such similarity in the case of trifluroperazine. In fact, trifluoperazine and haloperidol act on dopaminergic structures of the striatum [4], but besides this, neuroleptics which are butyrophenone derivatives (haloperidol, droperidol), like tranquilizers of the benzodiazepine series, potentiates GABA-ergic inhibition in the cerebral cortex [7, 9]. A GABA-positive action at the cortical level is not characteristic of trifluoperazine. This difference in the present investigation is evidently the potentiation by haloperidol of depression of the testing response caused by phenazepam in the recovery cycles of the primary response, and the absence of this effect with trifluoperazine. Interaction at the level of cerebral cortical GABA-ergic receptors can evidently explain the greater effectivness of haloperidol than of trifluoperazine in strengthening the anticonvulsant and also, probably, the anxiolytic action of phenazepam.

Since the antagonism with metrazol test can be used to predict tranquilizing activity [3], it can be tentatively suggested that at least in certain cases a combination of phenazepam with haloperidol may be more effective in the treatment of patients with neuroses than a combination of phenazepam with trifluoperazine.

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