EFFECT OF SOME CHOLINOLYTICS ON EXPERIMENTAL CATATONIA

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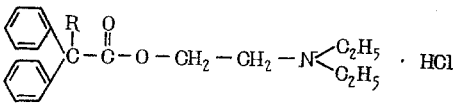
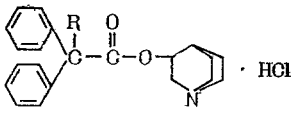
Experimental catatonia is a convenient model for studying the action of certain neurotropic drugs. A model of catalepsy produced in rats by phenothiazine derivatives has been suggested [4] for use in the selection of antidepressive preparations. Morpurgo [5] considers that cholinolytic preparations effective in the treatment of parkinsonism prevent the manifestation of phenothiazine catatonia in rats.

The authors used experimental catatonia to study five cholinolytics, four of which [amizil (benactyzine hydrochloride) and aprophen (its methy derivative), 3-hydroxyquinuclidine benzilate, and its methyl derivative, aprolidine] are tertiary amines possessing central and peripheral cholinolytic activity, while the fifth—metacin (oxyphenonium bromide)—is a quaternary ammonium salt acting selectively on the peripheral muscarine-like cholinergic systems; amizil and aprophen are the benzilate and diphenylpropionate of 2-double ring system of 3-hydroxyquinuclidine (see formulas).

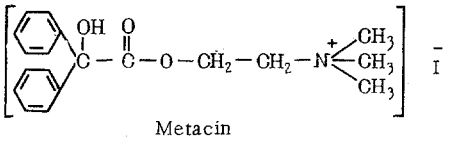


Amizil R=OH, Aprophen R=CH_3



3-hydroxyquinuclidine benzilate R=OH

Aprolidine R=CH_3



Metacin

The object of the investigation was to demonstrate that these cholinolytics possessed an anticatatonic effect which depended on their chemical structure, and also to determine whether this effect was dependent on central or cholinolytic activity.

EXPERIMENTAL METHOD

Experiments were carried out on albino rats weighing 130-140 g. Catatonia was induced by injecting Compazine (prochlorperazine) intraperitoneally in a dose of 5 mg/kg. The degree of catatonia was determined by the method described previously [5, 6]. Inability to take the forelimb from a step 3 cm high was assessed as $\frac{1}{2}$ point, and from a step 9 cm high—as one point. After injection of Compazine in this dose, all the animals developed catatonia, which reached maximal severity (three points for each rat) during the first hour and persisted for 6-7 h. The preparations to be tested were injected intraperitoneally into the rat 15 min before injection of the Compazine. Each test was carried out on a group of 4 rats. The maximal score of catatonia for the group was 12 points.

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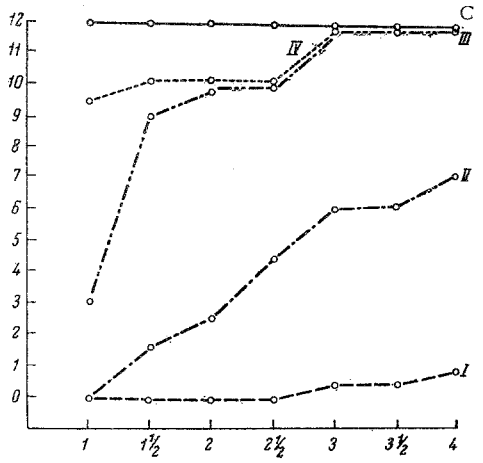

Fig. 1. Effect of preparations on catatonia produced in rats by Compazine. C) control; Compazine (5 mg/kg); I) 3-hydroxyquinuclidine benzilate (2 mg/kg) + Compazine (5 mg/kg); II) aprolidine (2 mg/kg) + Compazine (5 mg/kg); III) amizil (2 mg/kg) + Compazine (5 mg/kg); IV) aprophen (2 mg/kg) + Compazine (5 mg/kg). Ordinate – degree of catatonia (in points), abscissa – time (in h).

EXPERIMENTAL RESULTS

The experiment showed that amizil, aprophen, 3-hydroxyquinuclidine benzilate, and aprolidine diminished Compazine catatonia in rats.

In a dose of 1 mg/kg all the preparations gave a well marked effect. The intensity and duration of the catatonia were reduced. The most active preparation was 3-hydroxyquinuclidine benzilate. The rats did not develop catatonia for 1.5 h after injection of the preparation and subsequent (15 min later) injection of Compazine. The catatonia index after 2 h was 1.5 (compared with 12 in the control, after 3 h it was 3, and after 4 h 3.5.

Aprophen and amizil were less active than 3-hydroxyquinuclidine benzilate. Aprophen had the weakest action: after 1 h the index was 7, and after 1.5 h – 12. The results of the experiments in which the preparations were given in a dose of 2 mg/kg are illustrated in the figure.

Metacin was injected in doses of 2 and 5 mg/kg. No change in the catatonia index was observed in any of these experiments.

The investigation showed that of the cholinolytic activity possessed well marked anticatatonic properties. The quaternary compound (metacin), with selective peripheral cholinolytic activity, possessed no anticatatonic action. Hence, the observed anticatatonic effect was associated with the influence of the drug on the central cholinergic structures.

Previous investigations [1-3] showed that in their peripheral cholinolytic activity and in certain indices of their central action (effect on motor activity), derivatives of 3-hydroxyquinuclidine (3-hydroxyquinuclidine benzilate and aprolidine) are more active than the corresponding esters of 2-diethylaminoethanol (amizil and aprophen). This same pattern was shown with regard to their anticatatonic action. The same is true of the activity of the benzilates compared with that of the diphenylproprionates: amizil was more active than aprophen and 3-hydroxyquinuclidine benzilate was more active in this respect than aprolidine. Of all the investigated compounds, the one with the strongest anticatatonic action was 3-hydroxyquinuclidine benzilate.

LITERATURE CITED

1. M. D. Mashkovskii and S. S. Liberman, Farmakol. i Toksikol., No. 4, 42 (1957).
2. M. D. Mashkovskii and K. A. Zaitseva, Farmakol. i Toksikol., No. 6, 679 (1957).
3. M. D. Mashkovskii and K. A. Zaitseva, Farmakol. i Toksikol., No. 6, 36 (1967).
4. J. R. Boissier and P. Simon, Thérapie, 18, 1257 (1963).
5. C. Morpurgo, Arch. Int. Pharmacodyn., 137, 84 (1962).
6. W. Wirth et al., Ibid., 115, 1 (1958).