THE SENSITIZING EFFECT OF ATROPINE TO ACETYLCHOLINE

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There is evidence suggesting that atropine, depending on its concentration (or dose), may not only depress cholinergic excitation, but may also strengthen it. This "paradoxical" effect of atropine has been observed in different objects and in different experimental conditions by many authors [1, 2, 5, 7, 8, 10].

It is a fact of special importance that atropine enhances cholinergic excitation when extremely small doses [1] or concentrations [5] are used. Since certain authors [2, 8] explain this effect of atropine by depression of cholinesterase, in our experiments we compared choline-sensitizing concentrations of the weak anticholinesterase substance atropine [4, 8, 9, 10] with concentrations of the strong cholinesterase inhibitor, neostigmine.

EXPERIMENTAL METHOD

Experiments were conducted on the isolated duodenum of the rat. A segment of duodenum was placed in a bath, with a capacity of 100 ml, filled with Tyrode solution, through which oxygen was bubbled. The temperature was maintained at 38° by means of a Heppler ultrathermostat. Exposure to acetylcholine continued for 30-60 sec. After determination of the effective concentration of acetylcholine, the isolated duodenum was exposed for 10 min to atropine or for 30 min to neostigmine, after which acetylcholine was added again in the concentration previously tested.

EXPERIMENTAL RESULTS

In agreement with Hazard's findings [5], atropine in concentrations of $1 \cdot 10^{-18}$ - $1 \cdot 10^{-16}$ strengthened the acetylcholine contractions of the isolated rat's duodenum (in individual experiments sensitization to acetylcholine was exhibited by atropine in concentrations of $1 \cdot 10^{-15}$, $1 \cdot 10^{-19}$, and $2 \cdot 10^{-20}$; lower concentrations of atropine had no effect on the action of acetylcholine). Sensitization persisted for a short time after the atropine had been washed out. As a rule, moreover, it was more marked during the 5-10 min after washing out, and disappeared only after repeated washing with Tyrode solution. In concentrations of $1 \cdot 10^{-10}$ (in individual experiments $1 \cdot 10^{-11}$) or higher, atropine depressed the acetylcholine effect (Fig. 1). Concentrations of atropine of $1 \cdot 10^{-12}$ - $1 \cdot 10^{-14}$ had no effect on acetylcholine contractions.

In another series of experiments it was found that the anticholinesterase drug neostigmine possesses a sensitizing effect to acetylcholine in higher concentrations than atropine. The minimal sensitizing concentration of neostigmine acting for 30 min was $1 \cdot 10^{-16}$ (Fig. 2).

Hence, atropine, depending on its concentration, is capable not only of abolishing the acetylcholine contractions of the duodenum, but also of strengthening them, and the sensitizing effect of atropine is exhibited at lower concentrations than in the case of neostigmine. For this reason it can hardly be attributed to an influence on the enzymic hydrolysis of acetylcholine. Competition for "nonspecific" receptors [3] may possibly play a part in the mechanism of the sensitizing effect of low concentrations of atropine. If atropine is able to block these receptors, this must lead to an increase in the amount of active acetylcholine reacting with the specific cholinoceptors.

Changes in the reaction of the cholinergic systems to acetylcholine may also be involved in the production of

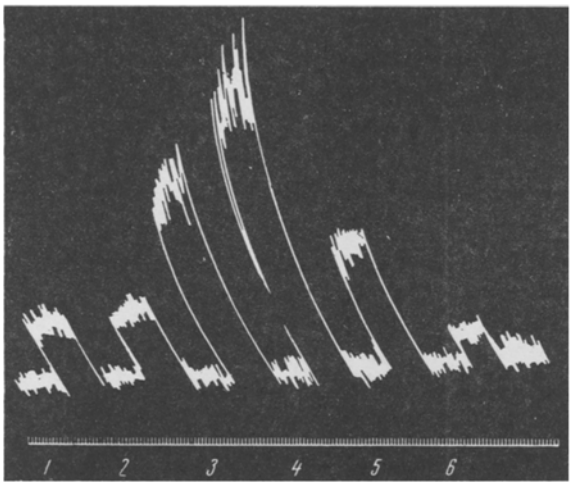

Fig. 1. Contractions of the isolated duodenum of a rat under the influence of acetylcholine ($1 \cdot 10^{-8}$). 1 and 2) Before action of atropine; 3) after exposure to atropine ($2 \cdot 10^{-18}$) for 10 min; 4 and 5) after washing out atropine for 5 and 60 min respectively; 6) after exposure to atropine ($2 \cdot 10^{-9}$) for 10 min.

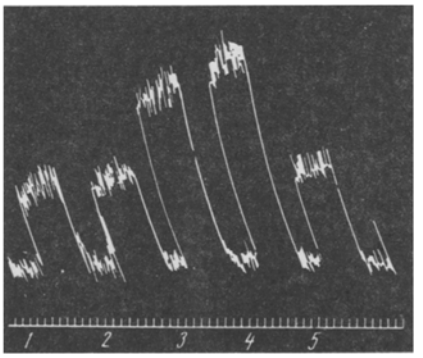

Fig. 2. Contractions of the isolated duodenum of a rat under the influence of acetylcholine ($1 \cdot 10^{-8}$). 1 and 2) Before action of neostigmine; 3 and 4) after exposure to neostigmine ($2 \cdot 10^{-16}$) for 30 min; 5) 1 h after washing out neostigmine.

this sensitizing effect of atropine: low concentrations of atropine may facilitate the interaction between the cholinergic systems and acetylcholine. This variant of the competitive relationships was first described by Haldane and Priestley in connection with oxygen and carbon monoxide, competing for hemoglobin [6]. According to their findings, small concentrations of carbon monoxide facilitate the reaction between hemoglobin and oxygen, while large concentrations prevent it. Similar relationships may be found in the case of the choline-sensitizing action of atropine.

SUMMARY

The author reproduced the experiments of Hazard showing the capacity of atropine (in a concentration of $2 \cdot 10^{-18}$) to enhance the acetylcholine contractions of the isolated rat intestine. The sensitizing effect of atropine is manifested in concentrations 1/100 as great as neostigmine. In the author's opinion this effect of atropine is analogous to the effect of low carbon monoxide concentrations, promoting the reaction between hemoglobin and oxygen in Haldane's experiments.

LITERATURE CITED

1. P. E. Dyablova. Fiziol. zh. SSSR 5, 491 (1958).
2. A. Ashford, G. B. Penn, and J. W. Ross, Nature (1962), v. 193, p. 1082.
3. D. Bovet and F. Bovet-Nitti. Farmakol. i toksikol. 3, 201 (1959).
4. W. Hardegg, E. Rilken, and H. Schmalz, Pflüg. Arch. ges. Physiol (1954), bd. 259, S. 317.
5. R. Hazard, E. Savini, and A. Renier-Cornec. Arch. int. Pharmacodyn. (1959), v. 120, p. 369.
6. J. S. Haldane and J. H. Priestley. Respiration [Russian translation], Moscow—Leningrad (1937).
7. B. Kisch Arch. exp. Path. Pharmak. (1926), Bd. 116, S. 227.
8. H. Lüllmann, Pharmacol, Ibid., (1952), Bd. 216, S. 152.
9. H. Lüllmann, W. Förster, and E. Westermann, Ibid., Bd. 215, S. 8.
10. R. Magnus, Pflüg. Arch. ges. Physiol. (1905), Bd. 108, S. 1.
11. M. H. Roepke, J. Pharmacol. exp. Ther. (1937), v. 59, p. 264.