EFFECT OF CHOLINOMIMETICS, BIOGENIC AMINES, AND THEIR ANTAGONISTS ON THE LOCAL ANESTHETIC EFFECT

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Many attempts have been made to connect the local anesthetic effect with the muscarine-like and nicotine-like cholinolytic activity of substances and their antihistamine or antiserotonin properties [2, 8, 11]. However, the experimental evidence concerning the cause of this relationship between local anesthetic activity of substances and their effect on reactive structures is extremely conflicting [compare 4, 5, 8, 11 and 3, 10, 12].

To determine the precise role of the reactive structures in the local anesthetic effect, in the present investigation the influence of pilocarpine, nicotine, histamine, serotonin, and adrenalin was studied on the terminal anesthesia of the cornea produced in guinea pigs by cocaine amethocaine, adiphenine, diphenhydramine, and promethazine.

EXPERIMENTAL

Experiments were carried out on 240 guinea pigs. The degree of terminal anesthesia was estimated by the method of Regniers [1]. The sensitivity of the cornea to tactile stimulation applied with a hair at the rate of 100 contacts per min was investigated every 5 min. In each investigation the minimal number of contacts to produce a corneal reflex was determined. The anesthesia was regarded as complete if no reflex was produced by 100 contacts. The sum of the numbers obtained over the period of 1 h gave the index of anesthetic action, or the Regniers index. All the test substances were used in aqueous solutions, and the duration of their contact with the retina was 3 min. Adrenalin (hydrochloride), pilocarpine (hydrochloride), nicotine (base), histamine (dihydrochloride), and serotonin (creatinine sulfate) were used in the form of a 6.1 mM solution, which was applied to the cornea for 3 min immediately before instillation of the solutions of the local anesthetics.

The relative anesthetic activity of the test substances was determined by Valette's formula [1].

EXPERIMENTAL RESULTS

The concentration–action curves for amethocaine and cocaine are shown in Fig. 1A.

Preliminary treatment of the cornea with a solution of pilocarpine hydrochloride slightly reduced the anesthetic activity of cocaine (Fig. 1B) but did not change the activity of amethocaine. Adrenalin had no effect on the anesthetic action of cocaine (Fig. 1D).

Nicotine, however, significantly reduced the anesthetic activity of cocaine (Fig. 1B) or amethocaine, but only when these anesthetics were used in high concentrations. Histamine and serotonin likewise reduced the anesthetic action of amethocaine and cocaine very significantly (Fig. 1C).

The fact, that preliminary treatment of the cornea with solutions of nicotine, histamine, and serotonin altered the slope of the concentration–action curve and lowered the maximum of anesthetic activity of cocaine and amethocaine, suggests that noncompetitive relationships exist between these local anesthetics, on the one hand, and nicotine, histamine, and serotonin on the other [6, 9].

The absence of competitive relationships between the local anesthetics and the substances listed above shows that the anesthetic effect of cocaine and amethocaine is not directly connected with their effects on nicotine-like cholinergic, histaminergic, or serotoninergic structures of the cornea, for the latter take part in the anesthetic action of these local anesthetics.

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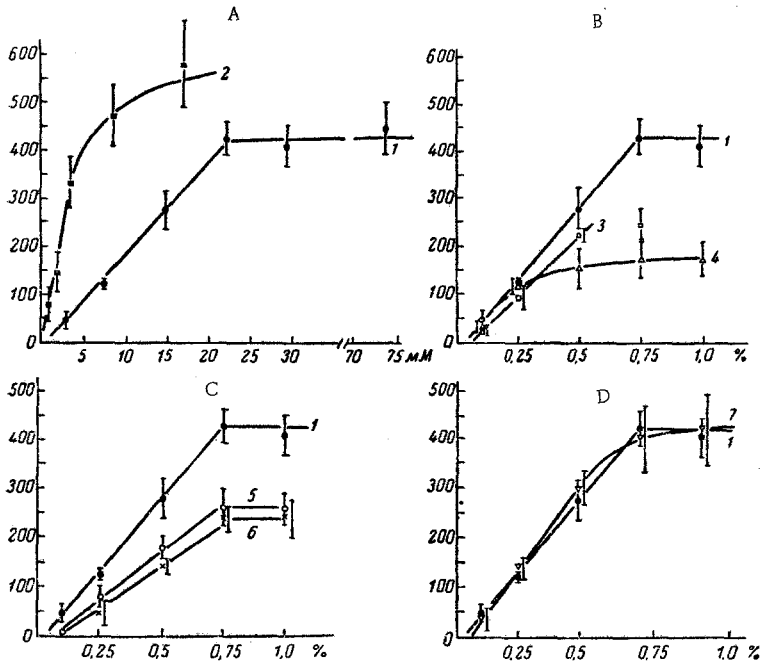

Fig. 1. Antagonism between cocaine and certain drugs when applied together to the cornea of a guinea pig. Abscissa: concentration of anesthetics in a molar scale for comparison of activity of substances (A); concentration of cocaine in percent (B-D). Ordinate: values of the Regniers index. Relationship between concentration and anesthetic activity of amethocaine (2) and cocaine (1); the same after treatment of the cornea with pilocarpine (3), nicotine (4), serotonin (5), histamine (6), and adrenalin (7).

Effect of Serotonin, Histamine, and Nicotine on Anesthetic Activity of Certain Substances

Substance	Activity of Solution of test substance after treatment of cornea with 6.1 mM solution of		
	serotonin	histamine	nicotine
Cocaine	0.68	0.56	0.6
Amethocaine	0.3	0.44	0.86
Adiphenine	0.8	0.8	0.48
Diphenhydramine	0.53	0.63	0.49
Promethazine	0.6	0.76	0.64

Note. The anesthetic activity of the substance in the control tests, i.e., without treatment with serotonin, histamine, and nicotine, was taken as 1.

The investigation of the effect of serotonin, histamine, and nicotine on the terminal anesthesia produced by the antagonists of these substances – promethazine, diphenhydramine, and adiphenine (hydrochlorides) – showed (see table) that serotonin most effectively reduced the anesthetic activity of amethocaine, diphenhydramine, and promethazine, while histamine was most effective against amethocaine, cocaine, and diphenhydramine, and nicotine was most effective against adiphenine and diphenhydramine.

The results of these experiments demonstrated that nicotine, serotonin, and histamine have the power to increase the sensitivity of the nerve endings of the cornea to adequate (mechanical) stimuli. This suggests that local anesthesia may be potentiated by the simultaneous use of local anesthetics and

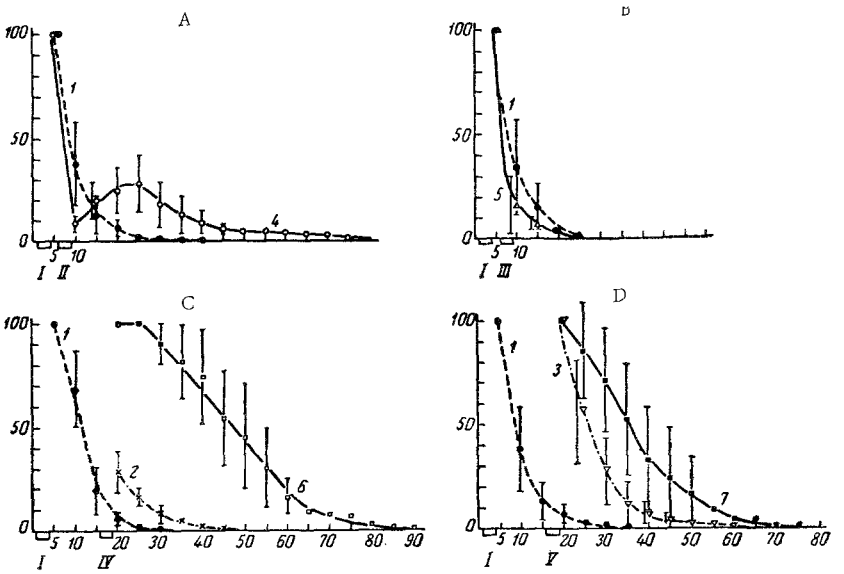

Fig. 2. Anesthetic effect of cocaine used in conjunction with certain other drugs. Abscissa: time (in min); ordinate: values of the Regniers index. Treatment of the cornea for 3 min with 0.5% cocaine solution (I), 0.1% BAS solution (II), 2% atropine solution (III), 0.24% promethazine solution solution (IV), and 0.05% amethocaine solution (V). Anesthetic activity in control tests of 0.5% cocaine solution (I), 0.24% promethazine solution (2), and 0.05% amethocaine solution (3). Anesthetic activity of cocaine used together with 0.1% BAS solution (4), 2% atropine solution (5), 0.24% promethazine solution (6), and 0.05% amethocaine solution (7).

antagonists of nicotine, serotonin, and histamine. Since, as was shown above, the antagonism between local anesthetics and nicotine, serotonin, and histamine is noncompetitive, it can be anticipated that potentiation of local anesthesia may be obtained by the use of local anesthetics together with antagonists of the above-mentioned substances, for the drugs which it is proposed to combine possess different (more accurately, not fully coincident) points of application of their action [7, 13, 14].

The experimental results confirmed these arguments. Application of solutions of dihydroergotoxin, diphenhydramine, and promethazine (Fig. 2C) or adiphenine for 3 min to the conjuntival sac 12 min after administration of cocaine, before the anesthesia was of a marked degree, potentiated the anesthesia to an extent which was greater than the combined action of the two substances. Meanwhile, when cocaine and amethocaine were combined in the same experimental conditions, the resultant effect was practically equal to the sum of the individual effects of the two substances (Fig. 2D).

The benzyl analogue of serotonin (BAS), when introduced into the conjunctival sac 2 min after administration of a 0.1% solution of cocaine (in this concentration BAS does not produce corneal anesthesia), essentially potentiated and prolonged the anesthetic effect of cocaine (Fig. 2A).

Atropine, when used in the same experimental conditions as a 2% solution, did not modify the anesthetic action of the cocaine (Fig. 2B), in agreement with results showing the weak action or even the total absence of action of pilocarpine on the anesthesia produced by cocaine or amethocaine.

The results of these experiments thus showed that changes in the functional state of the nicotine-like cholinergic, histaminergic, and serotoninergic structures of the sensory nerve endings of the cornea in the guinea pig, modify the degree and duration of the terminal anesthesia of the cornea produced by cocaine or amethocaine.

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