RELATIONS BETWEEN MEDIATOR RECEPTORS IN ENDINGS OF CORNEAL AFFERENT NERVES

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UDC 612.822.2-088.1

In response to local application of substances with mediator action (adrenalin, acetylcholine, histamine) and substances blocking specific receptors (dihydroergotoxin, inderal, atropine, and, by subcutaneous injection, diphenhydramine) together with amethocaine, mediator receptors capable of influencing one another were discovered in the cornea. Pharmacological analysis showed that corneal sensory nerve endings contain two systems of receptors, connected by reciprocal inhibitory relations, as a result of which they can regulate processes of excitation and inhibition in the sensory nerve ending.

KEY WORDS: cornea; mediator receptors; amethocaine anesthesia.

The cornea contains afferent fibers and their endings as well as endings and fibers of sympathetic and parasympathetic nerves [2, 3, 5, 6, 9]. The presence of mediators of adrenergic and cholinergic nerves and also of specific enzymes participating in the metabolism of these mediators has been demonstrated in the cornea [16-18]. One of the functions of the autonomic nervous system in the cornea is regulation of the functional state of the endings of afferent nerve fibers [1, 4, 7, 8, 11-15].

The object of this investigation was to study relations between corneal receptors.

EXPERIMENTAL METHOD

Inhibition of sensitivity was induced with amethocaine and assessed by the appropriate indices of anesthesia by Régnier's method [19]. Weakening of this inhibitory process was regarded as the result of the development of excitation. Experiments were carried out on the rabbit cornea. The sensitivity of the cornea was determined with the No. 10 Frey's bristle [10].

To study the role of mediator receptors in the development of inhibition and excitation in afferent nerve endings substances stimulating and blocking them specifically were used. The indicators themselves, in the concentrations used, did not induce anesthesia. All the substances tested except diphenhydramine were applied to the cornea at intervals of 2 min. Diphenhydramine was injected subcutaneously in a dose of 10 mg/kg 50 min before instillation of the solutions into the eyes.

EXPERIMENTAL RESULTS AND DISCUSSION

Blocking muscarinic (M) cholinergic receptors with atropine potentiated the anesthetic effect of amethocaine (Fig. 1: 1, 4, 5). Excitation of the M-cholinergic receptors with acetylcholine reduced the anesthetic action of amethocaine (Fig. 1: 1, 2, 3). The action of acetylcholine was abolished by atropine (Fig. 1: 3, 6). These results suggest that the sensory nerve endings of the cornea contain M-cholinergic receptors.

The excitability of the corneal M-cholinergic receptors depended on the state of the histamine receptors. For instance, after preliminary blocking of the histamine receptors by diphenhydramine, the effect of acetylcholine (Fig. 1: 3, 7) was considerably reduced. Acetylcholine thus probably exerts its weakening

Department of Pharmacology, Pharmaceutic Faculty, I. M. Sechenov First Moscow Medical Institute. [Presented by Academician P. K. Anokhin (deceased).] Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 79, No. 4, pp. 16-18, April, 1975. Original article submitted October 15, 1974.

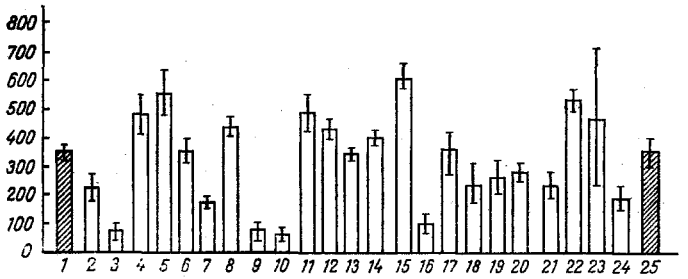

Fig. 1. Anesthetic action of 0.2% amethocaine solution combined with substances affecting adrenergic, histaminergic, and M-cholinergic receptors. Abscissa: 1) amethocaine (0.2%); 2) amethocaine (0.2%) +acetylcholine (0.01%); 3) amethocaine (0.2%) +acetylcholine (1%); 4) atropine (0.5%) +amethocaine (0.2%); 5) atropine (1%) + amethocaine (0.2%); 6) atropine (1%) +amethocaine (0.2%) + acetylcholine (1%); 7) diphenhydramine (10 mg/kg) +amethocaine (0.2%) +acetylcholine (1%); 8) adrenalin (0.01%) + amethocaine (0.2%) +acetylcholine (0.01%); 9) amethocaine (0.2%) +histamine (0.1%); 10) amethocaine (0.2%) +histamine (0.03%); 11) diphenhydramine (10 mg/kg) +amethocaine (0.2%); 12) diphenhydramine (10 mg/kg) +amethocaine (0.2%) + histamine (0.1%); 13) atropine (1%) +amethocaine (0.2%) +histamine (0.03%); 14) adrenalin (0.01%) + amethocaine (0.2%) + histamine (0.1%); 15) adrenalin (0.01%) +amethocaine (0.2%); 16) dihydroergotoxin (0.01%) +amethocaine (0.2%); 17) dihydroergotoxin (0.01%) +adrenalin (0.01%) +amethocaine (0.2%); 18) atropine (0.5%) +dihydroergotoxin (0.01%) +amethocaine (0.2%); 19) diphenhydramine (10 mg/kg) +dihydroergotoxin (0.01%) + amethocaine (0.2%); 20) diphenhydramine (10 mg/kg) +atropine (0.5%) +dihydroergotoxin (0.01%) +amethocaine (0.2%); 21) inderal (0.01%) + amethocaine (0.2%); 22) inderal (0.01%) + adrenalin (0.01%) + amethocaine (0.2%); 23) atropine (0.5%) + inderal (0.01%) + amethocaine (0.2%); 24) inderal (0.01%) + dihydroergotoxin (0.01%) + amethocaine (0.2%); 25) diphenhydramine (10 mg/kg) + atropine (0.5%) + inderal (0.01%) + dihydroergotoxin (0.01%) + amethocaine (0.2%). Ordinate: indices of anesthesia. Vertical lines on columns show confidence limits for P = 0.05.

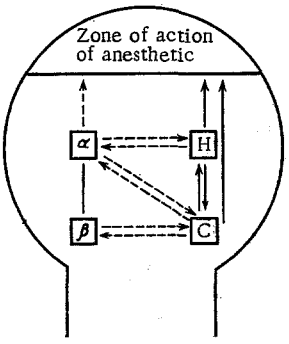

Fig. 2. Relations between α- and β-adrenergic, M-cholinergic and histaminergic receptors of the cornea and their influence on the zone of action of a local anesthetic. Continuous arrows show excitatory effect of receptors inhibitory effect of receptors on one another and on zone of action of anesthetic. α and β stand for α- and β-adrenergic receptors respectively; H) histaminergic, C) cholinergic receptor.

effect on the anesthetic action of amethocaine as a result of the excitation of histamine receptors and also of the stimulant effect of M-cholinergic receptors on the zone of action of the local anesthetic (Fig. 2).

Adrenalin completely prevented the manifestation of the weakening effect of acetylcholine on amethocaine anesthesia (Fig. 1: 2, 8). This action of adrenalin can be explained by its inhibitory effect on the zone

of action of the local anesthetic through excitation of α-adrenergic receptors, and also by its inhibitory effect on both histaminergic and M-cholinergic receptors (Fig. 2).

Histamine greatly weakened the anesthetic action of amethocaine (Fig. 1: 1, 9, 10). Subcutaneous injection of diphenhydramine potentiated the anesthetic effect of amethocaine (Fig. 1: 1, 11). Histamine did not weaken the amethocaine anesthesia after subcutaneous injection of diphenhydramine (Fig. 1: 9, 12). These experiments point to the existence of histaminergic receptors in the cornea. The decrease in the anesthetic effect of amethocaine under the influence of histamine could be due both to the direct excitatory effect of histaminergic receptors on the zone of action of the anesthetic and to the increased sensitivity of the M-cholinergic receptors to the excitatory action of acetylcholine. An inhibitory effect of histaminergic receptors and inhibitory α-adrenergic receptors is also a possibility (Fig. 2). Both atropine and adrenalin, in fact completely prevented the weakening action of histamine on amethocaine anesthesia (Fig. 1: 10, 13 and 9, 14).

Experiments in which adrenalin, the α-adrenergic blocking agent dihydroergotoxin, and the β-adrenergic blocker inderal were used gave evidence of the presence of α- and β-adrenergic receptors in the cornea (Fig. 1: 1, 15, 16, 17, 21). Excitation of the adrenergic receptors by adrenalin caused a marked increase in the anesthetic effect of amethocaine. Dihydroergotoxin sharply and inderal moderately reduced the anesthetic effect of amethocaine. Adrenergic receptors evidently interconnect with histaminergic and M-cholinergic receptors. Blocking the M-cholinergic receptors with atropine (Fig. 1: 16, 18) and the histaminergic receptors by diphenhydramine (Fig. 1: 16, 19), for instance, reduced the weakening action of dihydroergotoxin on amethocaine anesthesia. Blocking M-cholinergic receptors with atropine restored the anesthetic action of amethocaine after blocking of the β-adrenergic receptors (Fig. 1: 1, 21, 23).

Blocking the β-adrenergic receptors with inderal reduced the weakening action of dihydroergotoxin on amethocaine anesthesia (Fig. 1: 16, 24); the sensitivity of the α-adrenergic receptors to dihydroergotoxin was evidently reduced under these circumstances and they were blocked by it to a lesser degree. Probably at the same time the inhibitory effect of the β-adrenergic receptors on M-cholinergic receptors was removed. As a result the system of M-cholinergic receptors and histaminergic receptors had an excitatory action on the cornea (Fig. 2).

The results of these experiments suggest that corneal afferent nerve endings contain two systems of mediator receptors with opposite actions. One system includes the α- and β-adrenergic receptors, with synergistic relations between them. This system favors the development of inhibition. The other system includes M-cholinergic and histaminergic receptors, also with synergistic relations between them, but favoring the development of excitation. The two systems of receptors are connected by reciprocal inhibitory relations (Fig. 2). During the simultaneous blocking of all mediator receptors of the cornea, the effect of amethocaine is unchanged (Fig. 1: 1, 25).

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