PARTICIPATION OF CENTRAL MUSCARINE-LIKE AND NICOTINE-LIKE CHOLINERGIC SYSTEMS IN ANTIDIURETIC EFFECT OF ACETYLCHOLINE

N. S. Sapronov

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Intravenous injection of central muscarine-like and nicotine-like cholinolytics suppresses the antidiuretic effect of acetylcholine injected into the internal carotid artery. In the author's opinion both muscarine-like and nicotine-like cholinergic systems are involved in the mechanism of the antidiuretic effect of acetylcholine.

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In the modern view the neurohypophysis is a system embracing the anterior hypothalamic nuclei, the supraoptico-hypophyseal tract, and the pars nervosa of the pituitary gland itself [7, 9, 10, 11, 16]. The work of S. V. Anichkov and A. A. Belous [1, 2, 5] has shown that cholinergic systems sensitive to nicotine are present in the posterior lobe (pars nervosa) of the pituitary. If acetylcholine is injected intravenously or into the carotid artery, it delays diuresis, an effect explained by its central action directly on the neurohypophysis and also by its reflex action from the carotid chemoreceptors [5, 6, 12-15]. In earlier experiments on rats I showed that both nicotine-like (N), and muscarine-like (M) cholinomimetics (nicotine, arecoline) give an antidiuretic effect [8].

The object of the present investigation was to study the effect of central M- and N-cholinolytics (metamizil* and diphacil†) on the delay of diuresis produced by intraarterial injection of acetylcholine.

EXPERIMENTAL METHOD

Twenty-four experiments were performed on 2 female dogs weighing 15 and 16 kg with the ureters exteriorized by L. A. Orbeli's method. Both common carotid arteries of these dogs were exteriorized in skin tubes, and all branches of the left artery (except the internal carotid) were ligated and the carotid sinus was denervated. Acetylcholine, injected into the common carotid artery, entered the brain along the internal carotid artery (if injected into the left common carotid artery) or was distributed throughout the system of vessels branching from the common carotid artery (external carotid artery, internal maxillary artery, internal carotid and occipital arteries). A water load (600 ml) was given before the investigation; the water was injected through a gastric tube. Urine was collected in 15-min samples for 3 h. Diuresis reached a peak after 45-60 min. Acetylcholine was injected 45 min after injection of water into the stomach. Initially the effect of acetylcholine after intravenous and intraarterial injection was compared. In later experiments acetylcholine was injected into the carotid artery 15-20 min after preliminary intravenous injection of the central M-cholinolytic metamizil and the N-cholinolytic diphacil.

EXPERIMENTAL RESULTS

The dose of acetylcholine capable of causing distinct inhibition of diuresis, when injected into the internal carotid and common carotid artery of the dogs, was 0.01 and 0.02 mg/kg, respectively. Acetylcholine produced the same inhibition of diuresis when injected intravenously in a dose of 0.13 mg/kg. If small doses

*Methyldiazyl: Hydrochloride of the 2-diethylamino-1-methylethyl ester of benzylic acid.
†Adiphenine hydrochloride.

Department of Pharmacology, Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, Leningrad (Presented by Active Member of the Academy of Medical Sciences of the USSR S. V. Anichkov). Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 65, No. 3, pp. 73-76, March, 1968. Original article submitted July 28, 1968.

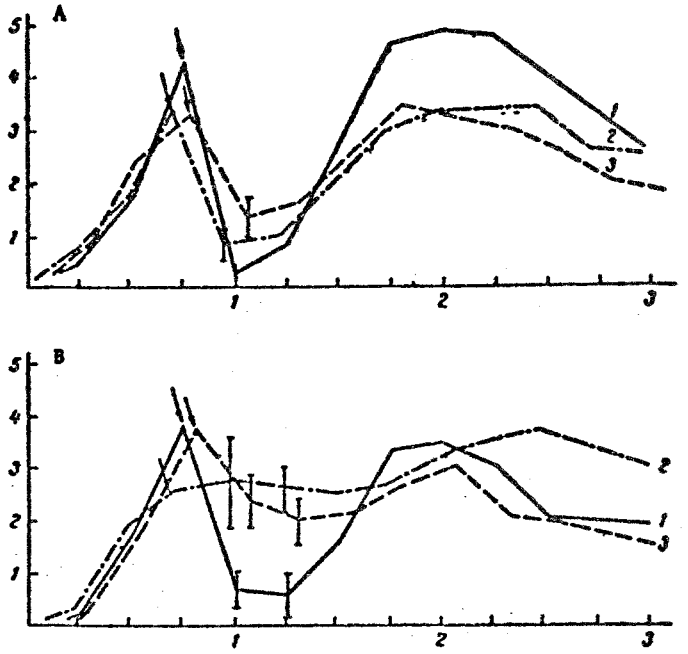

Fig. 1. Effect of acetylcholine and central cholinolytics on water diuresis. A) Injection of acetylcholine into common carotid artery: 1) acetylcholine (0.02 mg/kg); 2) metamizil (0.05 mg/kg) + acetylcholine (0.02 mg/kg); 3) diphacil (3.5 mg/kg) + acetylcholine (0.02 mg/kg); B) injection of acetylcholine into internal carotid artery: 1) acetylcholine (0.01 mg/kg); 2) metamizil (0.05 mg/kg) + acetylcholine (0.01 mg/kg); 3) diphacil (3.5 mg/kg) + acetylcholine (0.01 mg/kg). Abscissa) time (in hours); ordinate) diuretic (in ml/min); the arrows denote injection of acetylcholine.

of acetylcholine were injected intravenously (0.02 mg/kg), no inhibition of diuresis was observed (Fig. 1A). After injection of acetylcholine into the dogs a transient quickening of the pulse, with slight salivation and licking were observed. If the injection was given into the common carotid artery with an undenervated carotid sinus, dyspnea also was observed.

Metamizil was used in doses having no effect on diuresis (0.05-0.1 mg/kg). Higher doses (0.2-0.3 mg/kg) inhibited diuresis, sometimes giving rise to motor excitation of the dogs, with stereotyped movements and barking. The effects of acetylcholine, when injected into the common and internal carotid arteries after a preliminary injection of metamizil, were different. If acetylcholine was injected into the internal carotid artery, metamizil diminished the antidiuretic action of acetylcholine by about half; in one of the experiments no antidiuresis developed (Fig. 1B). If acetylcholine was injected into the common carotid artery after preliminary injection of metamizil the antidiuretic effect of the acetylcholine was only very slightly reduced (Fig. 1A). The dogs always developed dyspnea under these conditions.

Diphacil, in a dose of 3.5 mg/kg, had no significant effect on the diuresis. With an increase in dose of diphacil to 5-7 mg/kg or more, an antidiuretic effect was observed. As Fig. 1 shows, diphacil reduced the antidiuretic effect of acetylcholine when injected either into the common or into the internal carotid artery of the dogs. Injection of acetylcholine after preliminary administration of diphacil did not cause dyspnea.

The results of the experiments with intravenous and intracarotid injection of acetylcholine are in agreement with Pickford and Watt's [15] conclusion that acetylcholine facilitates the secretion of ADH by a central route. A. A. Belous found that relatively small doses of acetylcholine act via the carotid chemoreceptors, while large doses may act directly on the neurohypophysis [5, 6]. Since dyspnea was observed in dogs after injection of acetylcholine into the common carotid artery, indicating excitation of the chemo-

receptors, the reflex effect of acetylcholine from the carotid chemoreceptors cannot be ruled out. However, the results of experiments with injection of acetylcholine into the internal carotid artery with a denervated sinus in doses only half the size of those injected into the common carotid artery undoubtedly demonstrate its effect on the neurohypophysis. Experiments with preliminary injection of the central M- and N-cholinolytics metamizil and diphacil showed that both cause a decrease of about 50% in the antidiuretic effect of acetylcholine injected into the internal carotid artery, but do not completely abolish it. This gives grounds for assuming that both M- and N-cholinergic systems participate in the secretion of ADH under the influence of acetylcholine. Taking into account the findings of S. V. Anichkov and A. A. Belous [1, 2, 5], indicating the presence of N-cholinolytics systems in the pars nervosa of the pituitary gland, it may be considered that the M-cholinergic systems participating in regulation of ADH liberation are localized in the hypothalamus. The antidiuretic effects of acetylcholine injected into the common carotid artery may also be explained by its reflex effect from the carotid chemoreceptors, which are N-cholinergic in nature, because this effect is inhibited more strongly by diphacil than by metamizil. This is also confirmed by the onset of dyspnea following injection of acetylcholine into the common carotid artery with an intact carotid sinus and by the possibility of preventing its onset by the preliminary injection of diphacil.

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