MUSCARINIC CHOLINERGIC BIOCHEMICAL SYSTEMS AND SERUM ANTIBODY FORMATION

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Changes in antibody titers in the sera of immunized mice depending on the functional state of muscarinic cholinergic biochemical systems were investigated with the aid of muscarinic cholinomimetic and cholinolytic agents. The experimental results demonstrated the effect of muscarinic cholinergic systems on antibody formation. Peripheral muscarinic cholinergic systems play a more important role in this process than the corresponding central systems.

The neuro-humoral system plays a universal role in the maintenance of homeostasis and, consequently, in the immunological protection of the body [1, 3, 6, 7, 9]. The study of the effect of neurotropic pharmacological agents on immunological phenomena is thus of both theoretical and practical interest.

Injection of pilocarpine, of eserine and pilocarpine, and also of acetylcholine after immunization has been shown to increase the titers of specific serum antibodies [2, 4, 5, 10], while injection of atropine either lowers the antibody titers or has no effect on them [8].

Since publication of these investigations scientific views on the nature of cholinergic transmission of nervous impulses have been broadened and deepened, and the scope for pharmacological action on cholinergic biochemical systems has been greatly increased. However, the effect of cholinergic drugs on the antibody-forming function has so far received little study. Yet an investigation of this type would shed light on the intimate mechanism by which the nervous system controls immunogenesis and would considerably enrich the pharmacology of drugs affecting cholinergic transmission of nervous impulses which are being extensively used in medical practice at the present time.

The object of the investigation described below was to study the role of central and peripheral muscarinic cholinergic systems in the immunological response of serum antibody formation.

EXPERIMENTAL METHOD

Four series of experiments were carried out on 80 albino mice weighing 18-20 g. The appearance of hemagglutinins in response to immunization of the mice with sheep's red cells was used as the index of the antibody-forming response. Each animal received an intraperitoneal injection of 0.2 ml of a 20% suspension of sheep's red cells in physiological saline.

The functional state of the central and peripheral muscarinic cholinergic systems was altered by subcutaneous injection of arecoline, benactyzine, and oxyphenonium daily for 7 days after immunization. Control animals received physiological saline. The mice were decapitated 7 days after immunization and the titers of antibodies causing agglutination of sheep's red cells were determined in their blood serum by the standard method [4].

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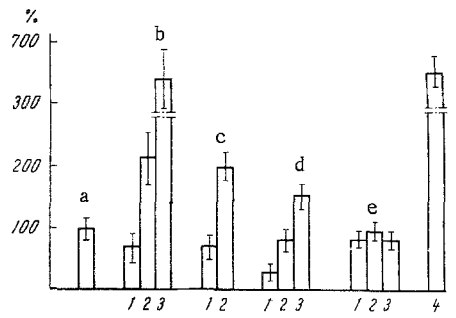

Fig. 1. Changes in titers of hemagglutinins produced by pharmacological excitation and blocking of muscarinic cholinergic systems: a) physiological saline; b) arecoline: 1) 5 mg/kg, 2) 10 mg/kg, 3) 12.5 mg/kg c) benactyzine: 1) 1 mg/kg, 2) 10 mg/kg; d) oxyphenonium: 1) 1 mg/kg, 2) 2 mg/kg, 3) 5 mg/kg; e) arecoline (10 mg/kg) 10 min after oxyphenonium: 1) 1 mg/kg, 2) 2 mg/kg, 3) 5 mg/kg; f) after benactyzine: 4) 1 mg/kg.

EXPERIMENTAL RESULTS

In the experiments of series I (Fig. 1b) the effect of the muscarinic cholinomimetic arecoline on the appearance of antibodies in the serum was investigated. The titer of hemagglutinins in the control for each series was taken as 100. Arecoline, in a dose of 5 mg/kg, gave an inconstant effect, for in some experiments it slightly reduced, while in others it increased the antibody titer. If arecoline was injected in doses of 10 and 12.5 mg/kg, i.e., in doses in which it had a definite excitatory action on muscarinic cholinergic systems, the antibody titers were consistently increased by 2-4 times.

In series II and III (Fig. 1 c,d) the effect of substances blocking muscarinic cholinergic systems on the antibody titer was investigated. Administration of the central cholinolytic drug benactyzine in a dose of 1 mg/kg, i.e., for practical purposes blocking only the central cholinergic systems, caused no significant change in the antibody titer. After administration of benactyzine in a dose of 10 mg/kg, leading to temporary blocking not only of the central, but also of the peripheral muscarinic cholinergic systems, the hemagglutinin titer was doubled. These results suggested that peripheral muscarinic cholinergic systems play a more important role in the antibody-forming response than the analogous systems of the brain. To verify this hypothesis experiments were carried out with the quaternary compound oxyphenonium, which selectively blocks peripheral muscarinic cholinergic systems. The results of the experiments with oxyphenonium in a dose of 1 mg/kg showed that during repeated blocking of the peripheral muscarinic cholinergic systems the hemagglutinin titer was several times lower than in the control.

The results of experiments in which oxyphenonium was given in a dose of 1 mg/kg were in good agreement with those of experiments in which arecoline was given in a dose of 10 mg/kg, for blocking and excitation of the muscarinic cholinergic systems had opposite effects on antibody formation. However, it was difficult on this basis to reconcile the results of the experiments with oxyphenonium and arecoline, on the one hand, with those of the experiments with benactyzine in a dose of 10 mg/kg on the other hand. Benactyzine in this dose stimulated antibody formation. When these results were compared with those of the other series of experiments it had to be assumed that the direction and degree of the effects produced by blocking the muscarinic cholinergic systems on the immunological response were dependent on the degree, duration, and extent of the blocking of these systems. This assumption was confirmed experimentally, by experiments in which oxyphenonium was given in doses of 2 and 5 mg/kg. The antibody titer after administration of this compound in a dose of 2 mg/kg did not differ significantly from that in the control, while after administration of oxyphenonium in a dose of 5 mg/kg, the titer was actually doubled.

It was concluded from these results that muscarinic cholinergic systems definitely participate in the antibody-forming response. Blocking these systems with anticholinergic drugs in small doses inhibits, but in large doses stimulates this immunological process. To investigate in more detail the degree to which central and peripheral muscarinic cholinergic systems participate in antibody formation the experiments of series IV were carried out (Fig. 1e) to study the effect of combined administration of the muscarinic cholinomimetic drug arecoline and the muscarinic cholinolytics benactyzine and oxyphenonium. To preserve only the central effect of arecoline (10 mg/kg) oxyphenonium (1 mg/kg) was injected 10 min before the arecoline was injected into the mice. When the experiments were carried out in this way the antibody titer was not increased. This suggested that the effect of arecoline in stimulating an increase in the antibody titer is due to its excitatory effect on the peripheral muscarinic cholinergic systems.

To test this hypothesis arecoline was injected against the background of the central muscarinic cholinolytic drug benactyzine (1 mg/kg). The antibody titer in the experimental mice in these experiments was 5 times higher than in the control, i.e., blocking of the central muscarinic cholinergic systems did not

prevent, but on the contrary facilitated the exhibition of the arecoline effect responsible for the increase in the antibody titer. This effect was consequently due to the excitatory effect of arecoline on peripheral muscarinic cholinergic systems.

The results of these experiments thus showed that excitation of peripheral muscarinic cholinergic systems facilitates an increase in the titers of specific serum antibodies. Excitation of the central muscarinic cholinergic systems, and equally their blocking, had no significant effect on the serum antibody titer. With an increase in the doses of anticholinergic drugs and strengthening of the blocking of the peripheral muscarinic cholinergic systems the response of antibody formation can be potentiated, and this result is probably due to the bringing into play of additional mechanisms for the nervous regulation of immunogenesis

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