PHARMACOLOGICAL ANALYSIS OF THE MECHANISM OF THE VASCULAR REACTION TO INTRA-ARTERIAL INJECTION OF HYPERTONIC SODIUM CHLORIDE SOLUTION

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The problem of the neurogenic or myogenic mechanism of vascular reactions in response to the rapid intra-arterial injection of hypertonic sodium chloride solution remains unsolved. Interest in this pressor vascular reaction (sometimes changing into depressor) is maintained by its similarity to the vascular reaction to stretching of the arterial system by an increase in intravascular pressure [6].

These reactions are known to be blocked by certain agents (Novocain, asphyxia, hypercapnia) not preventing the action of adrenalin and noradrenalin. At the same time, the vascular reaction to hypertonic NaCl solution persists after administration of ganglion-blocking agents (experiments of Konradi and Musyashchikova and experiments of Vil'de). This fact is evidence against the participation of peripheral reflexes relayed through the autonomic ganglia in this reaction.

It may be assumed, however, that the pressor reaction to intra-arterial injection of 20% NaCl solution is dependent not on a reflex relayed through the synapses of the ganglia, but on the action of this stimulus on the efferent nerve fibers or on the peripheral chromaffin cells. To verify this hypothesis, an attempt was made to study the effect of pharmacological agents blocking adrenergic or cholinergic mediation on this vascular reaction. The results of these investigations are described below.

EXPERIMENTAL METHOD

In acute experiments on 53 cats weighing 2-4 kg and anesthetized with urethane (1.2 g/kg), the reactions of the arterial pressure to maximally fast injection of 20% NaCl solution (0.5 ml/kg) into the central end of the femoral artery were studied.

The pressure in the carotid artery was recorded by a type EM-2 electromanometer on a type N-700 loop oscillograph. The pharmacological agents were injected intravenously from a syringe. Bilateral vagotomy and ligation of both carotid arteries were performed on the animals 30-40 min before the experiment began.

In six experiments the reaction of the vessels to injection of 20% NaCl solution were studied when the arterial pressure was lowered as a result of bleeding (1.5% of the body weight). In 12 experiments, the effect of dihydroergotoxin (DET; 0.3 mg/kg) on the fast intra-arterial injections of 20% NaCl solution was studied. The criterion that the action of the DET was complete was the absence or reversal of the pressor effect of adrenalin [1, 2, 5, 7]. This effect of blocking the adrenergic structures appeared 10-15 min after the beginning of action of the DET and persisted for more than 1.5 h after its injection.

Reserpine (Rausedil, 1% solution, manufactured by Gedeon-Richter) was injected intravenously (2.5 mg/kg) one in the course of the experiment (10 experiments), (and intraperitoneally 2.5 mg/kg) on two successive days (3 experiments). After receiving two doses of reserpine, the animals became lethargic and often were in a state of complete prostration. They developed bradycardia, disturbances of the gastrointestinal tract and of heat metabolism, and often paralysis of the hind limbs [4, 8]. The criterion that the action of reserpine was complete was absence of the pressor effect of ephedrine injected intravenously in a dose of 5 mg per animal [3, 9].

In experiments with atropine the completeness of its action was determined by disappearance of the effect of electrical stimulation by current from a type EI-1 stimulator (25 cps, 0.1 msec, 1 mA) of the peripheral end of the vagus nerve and by absence of the depressor effect of intravenous injections of

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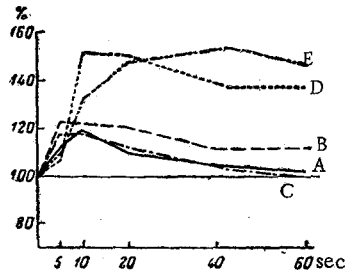

Fig. 1. Changes in arterial pressure in response to intra-arterial injection of 20% NaCl solution in a dose of 0.5 ml/kg (A) and in response to the same procedure after injection of DET (B) or atropine (C), after bleeding (D), and against the background of a lowered arterial pressure after injection of serpine (E).

acetylcholine (10 and 100 μg). Atropine, in a dose of 100-1000 μg, completely blocked the action of 10 μg, and reduced the depressor effect of 100 μg of acetylcholine. After intravenous injection of atropine (100-4000 μg), the effect of the vagus nerve on the heart and blood pressures was completely abolished.

EXPERIMENTAL RESULTS AND DISCUSSION

Control experiments (6) with repeated, rapid intra-arterial injection of 20% NaCl solution showed that after the 1st-5th injection, the pressor reaction was constant and persisted for more than 1 min, changing after the 11th-15th injection into a depressor reaction. For this reason not more than five injections of hypertonic NaCl solution were given in the course of the experiment.

When 60 sec had elapsed after injection of DET (0.3 mg/kg), lowering the blood pressure to 52±5% of its original level (mean value 118 mm) not only did the amount of increase of the arterial pressure in response to injection of 20% NaCl solution not diminish, but it actually increased slightly (see Fig. 1). Whereas, before injection of DET, the maximal increase of arterial pressure after the intra-arterial injection of 20% NaCl solution was 119.4±3.7% after 10 sec and 105.4±2.6% of the initial level after 40 sec, the value of this index after injection of DET was 122±5.2% and 112±8.7% respectively. The mean initial pressure before injection of DET was 118±9 mm and 94±7 mm after injection.

The intravenous injection of reserpine (2.5 mg/kg) lowered the blood pressure on the average by 49±5.3 mm (initial level 132 mm). After a single injection of reserpine in response to the intra-arterial injection of 20% NaCl solution, the character of the pressor reaction was maintained (maximal increase of blood pressure 11±1.7 mm), while after 40 sec this reaction changed into a depressor reaction (−9.2±1.8 mm). These experiments are illustrated in Fig. 1C, D. Similar results were obtained in experiments with the preliminary intraperitoneal injection of reserpine. In two experiments, after its injection, the reaction to intra-arterial injection of 20% NaCl solution was reproduced after preliminary bleeding (1.5% of the body weight) and was compared with the reaction of the vessels to intra-arterial injection of 20% NaCl solution, also carried out against the background of an arterial pressure lowered by bleeding (6 experiments) before injection of the solution. As Fig. 1 shows, when the arterial pressure was lowered, the pressor reaction to intra-arterial injection of 20% NaCl solution was considerably increased in strength both before and after injection of reserpine.

After the intravenous injection of atropine (500-1200 μg), causing practically no change in the blood pressure, the reaction of the vessels to the intra-arterial injection of 20% NaCl solution was almost indistinguishable from that found before blocking of the muscarine-like cholinergic system (see Fig. 1C). Admittedly this reaction developed rather more slowly than before the injection of atropine. After injection of 150-300 μg atropine this reaction was practically indistinguishable from the preceding reaction.

The persistence of the pressor effect caused by rapid injection of hypertonic NaCl solution into the central end of the femoral artery after blocking of the adrenergic mechanisms by DET and reserpine showed that these mechanisms play little or no part in the reaction under investigation.

On the basis of their experiments, Burn and Rand suggest that the sympathetic fibers themselves (and not only their effectors), may be stimulated by an adrenergic mechanism. The persistence of the vasoconstrictor reaction after injection of atropine indicates that in the case under consideration this mechanism likewise cannot play an important role.

The experiments further showed that against the background of blocking of the pressor action of adrenalin by DET the reactions to fast intra-arterial injections of 20% NaCl solution remained pressor and actually increased slightly in magnitude.

Consequently, the vascular reaction to the rapid intra-arterial injection of 20% NaCl are connected with neither adrenergic nor cholinergic mechanisms. There is, therefore, very little evidence for assuming that any peripheral nervous mechanism is involved in this vascular reaction. Although G. P. Konradi

submitted as one of his hypotheses that the vessels of a mechanism of peripheral reflex type participate in the reaction under consideration [6], the results of the experiments described in this paper and carried out at Konradi's suggestion make this conclusion extremely improbable.

The reaction of the smooth musculature of the vessels to hypertonic NaCl solution, and also, probably, its reaction to stretching are evidently more correctly regarded as myogenic.

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