DISTURBANCES OF MEMBRANE PROCESSES IN VASCULAR SMOOTH MUSCLE AS A POSSIBLE CAUSE OF SPASM OF THE INTERNAL CAROTID ARTERY

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During resistography of the internal carotid artery, isolated in situ in dogs and perfused with Ringer–Krebs bicarbonate solution, depolarization of the muscle membranes of the tunica media, evoked by an increase in the K^+ concentration in the perfusion fluid or by intraarterial injection of ouabain, led to prolonged contraction of the vessel wall resembling spasm. This effect persisted after intra-arterial injection of Hydergine, methysergide, and reserpine, but it was abolished if the artery was perfused with a Ca^{++}-free solution containing EDTA. During partial depolarization of the muscle membranes the vasoconstrictor effect of serotonin on the artery increased and became more prolonged. It is concluded that a disturbance of the state of the muscle membranes may be one cause of spasm of the internal carotid artery under natural conditions.

In the analysis of contractile processes in the tunica media of blood vessels isolated strips of large arteries of elastic type [9, 12] or the whole vascular system of isolated organs, containing vessels with different types of functions [10, 11], are usually used. The technique of resistography of the internal carotid artery isolated in situ in dogs, as recently developed [3], has made it possible to analyze processes lying at the basis of the onset of spasm in arteries of muscular type [1], while their nervous connections remain intact.

The object of the investigation described below, a continuation of previous studies of the mechanisms of vascular spasm [2, 3, 5, 6], was to elucidate the role of depolarization of the muscle cell membranes in the tunica media of blood vessels during the development of spasm of the internal carotid artery.

EXPERIMENTAL METHOD

Experiments were carried out on 25 dogs of different breeds superficially anesthetized with urethane (approximately 40 mg/kg, intraperitoneally, 6-7 h before the beginning of the experiment). Resistography of the hemodynamically isolated internal carotid artery, left in situ with its nerve supply intact, and perfused with Ringer–Krebs bicarbonate solution, was carried out. To begin with all anastomoses of this artery with the system of the external carotid artery were occluded, while inside the skull a thin polyethylene catheter was introduced into the artery (through the middle cerebral artery) so that the perfusion fluid could escape without having to pass through the other cerebral vessels [3, 4]. The artery to be investigated was perfused by a constant output pump with a solution of the following composition, oxygenated and warmed to 37°C: NaCl 0.69%, KCl 0.035%, $CaCl_2$ 0.028%, KH_2PO_4 0.016%, $MgSO_4 \cdot 7H_2O$ 0.029%, glucose 0.05%; pH 7.4. The conditions of perfusion of the artery were constant and the blood vessel wall remained in a satisfactory state (especially its responses to each type of stimulus used) during the acute experiment which lasted 4-5 h.

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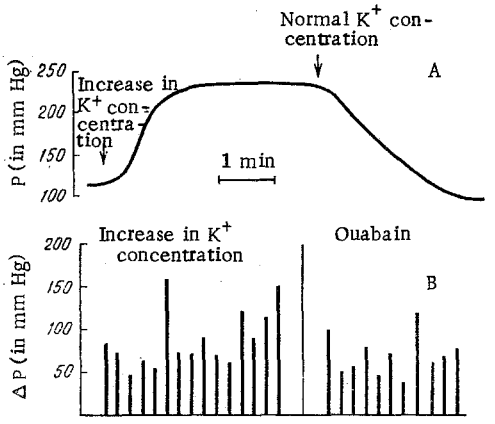

Fig. 1

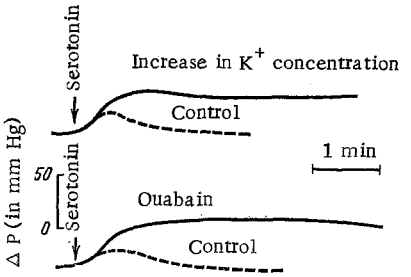

Fig. 2

Fig. 1. Prolonged contraction of the wall of the isolated internal carotid artery of a dog during membrane depolarization of the smooth muscle cells of the vessel wall: A) increase in perfusion pressure in artery in response to a fivefold increase in the K^+ concentration in the perfusion fluid compared with normal; B) constrictor effect in individual experiments in response to an increase in the K^+ concentration in the perfusion fluid; C) the same after intra-arterial injection of ouabain (1 mg).

Fig. 2. Changes in constrictor effect of serotonin on internal carotid artery of a dog isolated in situ in response to partial depolarization of muscle membranes of the tunica media of the vessel and an increase in the K^+ concentration in the perfusion fluid (above) or after injection of ouabain (1 mg) into the artery (below). Broken line shows changes in perfusion pressure in response to injection of serotonin during perfusion of the artery with normal Ringer–Krebs solution.

The substances to be tested were either injected over a period of 10 sec into the perfusion fluid supplied to the artery or they were dissolved in the perfusion fluid and acted on the arterial wall for a long time. In the case of a change in the concentration of particular ions, the perfusion fluid was kept isoosmotic by addition or subtraction of other ions (for example, an increase in the K^+ concentration was compensated by a corresponding decrease in the Na^+ concentration).

EXPERIMENTAL RESULTS

Depolarization of the muscle membranes was produced either by increasing the K^+ concentration in the perfusion fluid [7, 9, 10, 12] or by injecting ouabain, a specific inhibitor of active ion transport, responsible for polarization of membranes [13], into the artery. With an increase of 4-5 times in the K^+ concentration in the perfusion fluid compared with initially, a sharp rise in the perfusion pressure took place, indicating an increase in the tone of the wall of the internal carotid artery, but after restoration of the initial composition of the perfusion fluid the original state of the arterial wall was quickly restored (Fig. 1A). The degree of increase in the perfusion pressure in different experiments is shown in Fig. 1B. The increase in hydraulic resistance of the vessel was 7.5 ± 2.3 mm Hg/ml/min, on the average 62% of its initial value. After complete removal of K^+ from the perfusion fluid, the opposite effect was regularly observed: the level of the perfusion pressure fell. Injection of ouabain (0.25 mg/ml over 10 sec) into the artery evoked an increase in the perfusion pressure (Fig. 1C) which lasted for tens of minutes. Against the background of K^+-induced vasoconstriction, ouabain caused a further increase in the resistance of the vessel (on the average by 4 mm Hg/ml/min).

The vasoconstrictor effect of K^+ persisted after preliminary injection of Hydergine (0.5-1 mg), methysergide (0.1 mg), and reserpine (2.5 mg) into the perfusion fluid, blocking serotoninergic and adrenergic receptors in the blood vessel wall. Consequently, the action of K^+ on the wall of the internal carotid artery was direct and not reflex. On the other hand, after perfusion of the artery for 15-20 min with a

Ca^{++}-free solution containing EDTA (ethylenediaminetetraacetate, binding Ca^{++}) in a dose of 40 mg per 100 ml perfusion fluid, the constrictor effect of K^+ and ouabain was abolished. The vasoconstrictor effect of drugs inducing membrane depolarization of the smooth muscle cells of the internal carotid artery thus involves the participation of Ca^{++}, like the effect of other vasoconstrictor agents [2, 12].

When the muscle membranes were to a large extent depolarized (as a result of an increase in the K^+ concentration or of injection of ouabain) and the arterial wall was contracted to its maximum, the effects of the vasoconstrictor drugs were considerably weakened or abolished altogether. However, against the background of partial depolarization (with a very slight increase in K^+ concentration or after injection of small doses of ouabain) the constrictor effect of serotonin [2, 4, 8] was increased and the subsequent relaxation of the vessel wall was considerably retarded (Fig. 2).

A disturbance of active ion transport, preventing repolarization of the membranes of muscle cells in the arterial wall after their contraction, may thus be one of the causes of spasm of the internal carotid artery. Under natural conditions this may depend on pathological or age changes in the membranes of the smooth muscle cells of the blood vessels, disturbance of enzyme reactions responsible for the active transport of Na^+ and K^+ through the muscle membranes, and disorders of other processes involved in membrane repolarization.

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