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ACTION OF PROSTAGLANDINS E_1 AND E_2 ON THE INTERNAL CAROTID ARTERY

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In experiments on the internal carotid artery of a dog isolated from the rest of the circulation, the following effects of prostaglandins (PG) E_1 and E_2 were discovered. PG E_1 caused either a constrictor or a dilator effect with habituation during repeated exposures, whereas PG E_2 had only a constrictor effect without any habituation. The duration of the effects of PG E_2, especially relaxation, was much longer than that of the effects of serotonin; residual contraction of the vascular smooth muscles was frequently observed; PG E_1 and PG E_2 potentiated the effects of serotonin and often of noradrenalin.

KEY WORDS: angiospasm; prostaglandins; internal carotid artery; serotonin; smooth muscles of blood vessels.

In the arterial system of the brain the most typical sites for the onset of spasm are the large arteries and, in particular, the internal carotid arteries [2]; for that reason investigations of the pathophysiological mechanisms of development of angiospasm are best carried out on these vessels. In the last decade the various prostaglandins (PG) have attracted considerable attention of investigators because of their possible role in the development of spasm of the cerebral arteries [9, 12, 13]. PG may have a direct action on the smooth muscles of arteries, by penetrating into their wall from the blood or from the medium surrounding the vessel, or if synthesized within the vessel wall itself.

The object of this investigation was to study the action of PG E_1 and E_2 on the internal carotid artery of the dog, isolated from the rest of the circulation; the work was a further development of the writers' studies of the role of these physiologically active substances in the development of pathological constriction, i.e., of angiospasm, in the brain [5].

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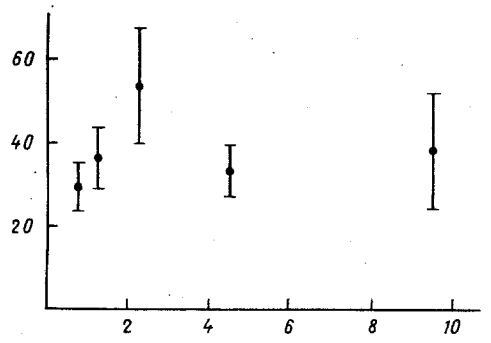

Fig. 1

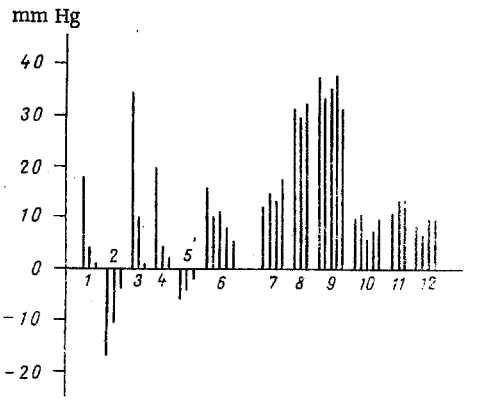

Fig. 2

Fig. 1. Magnitude of constrictor action of PG E_2 on dog carotid artery isolated from remainder of circulation. Abscissa, dose of Pg E_2 (in μg); ordinate, increase of perfusion pressure (in mm Hg).

Fig. 2. Changes in constrictor action of PG E_1 (1-6) and PG E_2 (7-12), expressed as increase of perfusion pressure (in mm Hg), during their repeated injection into dog internal carotid artery isolated from rest of circulation.

EXPERIMENTAL METHOD

Experiments were carried out on the internal carotid artery, isolated from the rest of the circulation, of 28 mongrel dogs of both sexes weighing 15-25 kg, anesthetized with pentobarbital (40 mg/kg, intraperitoneally). The technique of circulatory isolation of the internal carotid artery was described in detail previously [3, 4]. The artery studied was continuously perfused under standard conditions (37°C) by means of a constant delivery pump with oxygenated Ringer–Krebs bicarbonate solution with glucose. From the perfusion pressure recorded it was possible to judge changes in the tone of the wall of this artery while in situ, with its innervation intact. PG E_1 and PG E_2 (from Upjohn, USA), like the other physiologically active substances, were injected under standard conditions (in a volume of 2 ml, over a period of 10 sec) into the perfusion fluid entering the test artery, and they were then collected and thus had no action on the other part of the vascular system. The experimental results were subjected to statistical analysis.

EXPERIMENTAL RESULTS

PG E_1 and PG E_2 differed in their action on the internal carotid artery. First, PG E_2 in all cases caused an increase in tone of the vascular smooth muscles; no definite relationship could be found between the magnitude of the effect and the dose of PG E_2 (Fig. 1). PG E_1 in most experiments (in a random sample in 42.5% of 141 tests) caused an increase in tone of the smooth muscles of the artery, and in the rest of the experiments it caused a decrease in tone, in general agreement with data in the literature [6-8]. Second, during repeated exposure to PG E_1 "habituation" of the vascular smooth muscles was usually observed to it; the magnitude of the effects gradually diminished, whereas during repeated exposure to PGE_2 this was not observed (Fig. 2).

After blockade of the α-adrenoreceptors in the arterial wall the constrictor effects of PG E_1 and PG E_2 not only were not abolished, but were usually increased. After administration of dihydroergotoxin (0.1 mg) their magnitude increased on average by $54 \pm 18\%$, whereas after administration of phenoxybenzamine (1 mg) it increased by $43.5 \pm 29.6\%$ of the initial value. This is evidence that these PG exert their constrictor action on the internal carotid artery in other ways than through adrenoreceptors. Reserpine considerably weakened the constrictor effects of Pg E_1 and PG E_2 – by about $73.2 \pm 9.8\%$, the same as those of PG A_1 and PG B_1 [5]. The effects of these PG were thus somehow connected with the mechanisms through which serotonin and catecholamine act on smooth muscles.

From the point of view of development of pathological constriction of the internal carotid artery, the character of relaxation of the vascular smooth muscles during the constrictor effects of PG is particularly interesting. Since a restrictor response of the internal carotid artery was constantly evoked by PG E_2, the following indices of its effect were determined: 1) The relative duration of the constrictor effect (independent of its magnitude) was calculated per mm Hg increase of perfusion pressure. It amounted to 15 ± 2 sec, compared with only 3.0 ± 0.3 sec for serotonin. 2) The relaxation index, showing the duration of relaxation as a

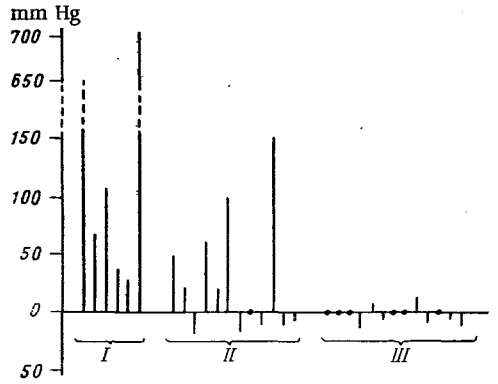

Fig. 3. Effect of PG E_1 and PG E_2 on constrictor action of serotonin (I), noradrenalin (II), and an increase in K^+ concentration in perfusion fluid (III) on dog internal carotid artery isolated from rest of circulation. Data given as percentages of initial effect (before action of PG).

percentage of the duration of constriction, taken as 100, was 372 ± 29 sec for PG E_2, whereas for serotonin it was much lower, namely 295 ± 21 sec. 3) The frequency of contracture, i.e., of residual contraction of the smooth-muscle membrane after the relaxation process had ended, in a random sample in 43 tests of the action of PG E_2 amounted to 58% of cases; the degree of increase of vascular tone compared with the initial background averaged 12.0 ± 2.2 mm Hg.

The characteristics of the constrictor action of PG E_2 on the internal carotid artery thus indicate that if this PG participates in the process of constriction of this artery under natural conditions, it is much more capable than serotonin of causing the development of spasm in the vessel [2], although the actual magnitude of the constrictor effect of PG E_2 is less than half of the effects of corresponding doses of serotonin.

From the standpoint of the role of PG of the E group in the development of spasm of the cerebral arteries the result of their action on the constrictor effects of other physiologically active substances and, in particular, of serotonin and catecholamines is also of considerable interest. The present experiments showed that after the end of the action of PG E_1 (irrespective of whether its effect was constrictor or dilator) and of PG E_2 (whose effect is always constrictor) the contractile action of serotonin on the smooth muscles of the artery was considerably increased (by 269 ± 133%), but the effect of noradrenalin was changed less considerably, and frequently in an inconstant direction: in some experiments it was increased, in others reduced; meanwhile the PG E_1 and E_2 had no definite effect on contraction of the arterial wall caused by depolarization of the plasma membranes of the smooth muscles in response to an increase in the K^+ concentration in the perfusion fluid (Fig. 3). The action of PG E_1 and PG E_2 thus differs from the effects of PG A_1 and PG B_2, which had a perfectly definite potentiating action on the effects of both serotonin and noradrenalin.

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