11. E. E. Muirhead, B. Brooks, J. A. Pitcock, et al., J. Clin. Invest., 51, 181 (1972).
12. C. Pace-Asciak, J. Biol. Chem., 250, 2795 (1975).
13. D. J. Pugsley et al., Circ. Res., 36, No. 6, Suppl. 1, 81 (1975).
14. P. Sirois and D. J. Gagnon, Experientia, 30, 1418 (1974).
15. L. Somova, Nephron, 8, 575 (1971).
16. C. V. Strong, R. Boucher, W. Nowaczynski, et al., Proc. Mayo Clin., 41, 433 (1966).
17. L. Tobian, M. Ishii, and M. Duke, J. Lab. Clin. Med., 73, 309 (1969).
18. L. Tobian, Am. J. Med., 52, 595 (1972).

POSSIBLE ROLE OF PROSTAGLANDINS A_1 AND B_1 IN SPASM OF THE INTERNAL CAROTID ARTERIES

G. I. Mchedlishvili and L. G. Ormotsadze

UDC 616.133.3-009.12-092:577.175.859

Experiments were carried out on the internal carotid artery of a dog, isolated from the rest of the circulation and continuously perfused in situ with oxygenated Ringer–Krebs bicarbonate solution. Prostaglandins A_1 and B_1 (PGA_1 and PGB_1) cause contraction of the artery. The effect of both prostaglandins was much less, but more prolonged, than the effect of the same doses of serotonin. The following facts are evidence of a possible role of prostaglandins in the development of angiospasm: a) In response to the repeated action of PGA_1 and PGB_1 their effect is unchanged and it therefore ought probably not to be reduced during the prolonged action of these prostaglandins on the vessel wall; b) PGA_1 and PGB_1 potentiate the constrictor effect of both serotonin and noradrenalin.
KEY WORDS: angiospasm; prostaglandins; internal carotid artery; serotonin; smooth muscles of blood vessels.

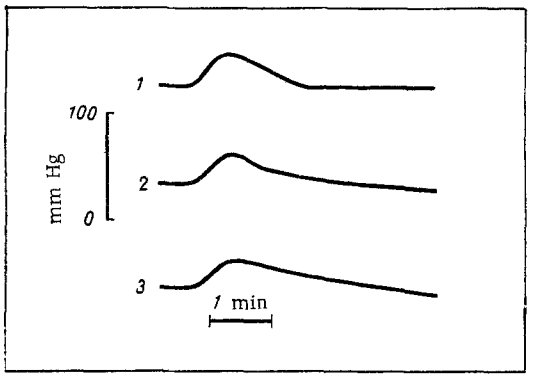
Although they were discovered more than 40 years ago the prostaglandins (PG) first attracted attention as physiologically active substances only in the 1960s. Unlike hormones produced by the glands of internal secretion, PG are formed in the cells of various tissues and they are regarded as "cell hormones." It has been suggested that PG are synthesized and broken down comparatively quickly and that their physiological effect is mainly local [1, 2]. Most PG (A_1, B_1, E_2, $F_{2\alpha}$) have a vasoconstrictor action, but some (mainly E_1, and inconstantly) have a vasodilator action [2, 12]. The constrictor effect of PG (A_1, E_2, and $F_{2\alpha}$) has also been demonstrated on the cerebral vessels; they were dilated by PGE_1 [3, 10, 11].

The object of this investigation was to study the action of PGA_1 and PGB_1 on the internal carotid artery which, if the behavior of different parts of the arterial system of the brain and the physiological mechanisms controlled by them [4] are taken into account, must be the most typical site of origin of angiospasm in the brain [5, 9].

EXPERIMENTAL METHOD

Experiments were carried out on 19 dogs in which the internal carotid artery was isolated from the rest of the circulation. The artery, remaining in situ and with its innervation intact, was perfused continuously with oxygenated Ringer–Krebs bicarbonate solution through a constant-output pump. The dynamics of the perfusion pressure thus reflected changes in the tone of the artery. Fuller details of the method were

Laboratory of Physiology and Pathology of the Cerebral Circulation, I. S. Beritashvili Institute of Physiology, Academy of Sciences of the Georgian USSR, Tbilisi. (Presented by Academician of the Academy of Medical Sciences of the USSR N. A. Fedorov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 83, No. 6, pp. 661-663, June, 1977. Original article submitted November 5, 1976.



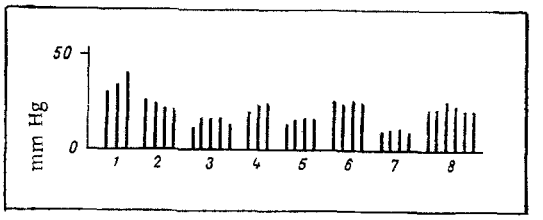


Fig. 1 Fig. 2

Fig. 1. Comparison of constrictor action of serotonin and of PGA_1 and PGB_1 on internal carotid artery of dog isolated from rest of circulation. If the dose of PGB_1 was 10 times greater and that of PGA_1 50 times greater than the dose of serotonin, constrictor effects were about equal (in mm Hg perfusion pressure). 1) Serotonin (0.1 μg), 2) PGA_1 (5 μg), 3) PGB_1 (1 μg).

Fig. 2. Absence of regular changes in constrictor effects after local action of PGA_1 (1-4) and PGB_1 (5-8) on internal carotid artery of dog isolated from rest of circulation. Increase in tone of wall after intraarterial injection of substances shown as increase of perfusion pressure (in mm Hg).

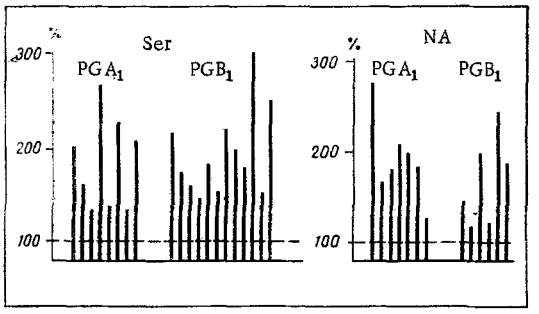


Fig. 3. Increase in constrictor action of serotonin (Ser) and noradrenalin (NA) on wall of internal carotid artery of dog isolated from rest of circulation (in percentage of initial, taken as 100) after action of PGA_1 and PGB_1.

described previously [7-9]. Like the other substances used, PGA_1 and PGB_1 (Upjohn Company, USA), were injected into the perfusion fluid entering the artery studied.

EXPERIMENTAL RESULTS

After intraarterial injection of PGA_1 (2-20 μg) and PGB_1 (0.5-5 μg) constriction of the internal carotid artery was constantly recorded. In response to equal doses of these PG the mean constrictor effect of PGB_1 was 325 ± 36% of the effect of PGA_1. The constrictor effects of both these PG were much less than that of serotonin (Fig. 1). This could be due either to differences in the number of receptors for these PG and serotonin in the membranes of the smooth-muscle cells of the artery or to the low permeability of those layers of the arterial wall that separate the lumen of the vessel from the smooth muscles for PG. If PG are formed under natural conditions in the region of the smooth muscles of the internal carotid artery, their action ought not to depend on the permeability of the intima of the vessels. However, permeability should have a significant role in the action of PG derived from the blood stream.

If PG and serotonin remained for the same length of time in the perfusion fluid of the artery the effect of PG lasted much longer than effects of serotonin of the corresponding magnitude: 313 ± 32% for PGA_1 and

467 ± 54% for PGB_1. In some cases, after contraction of the smooth muscles produced by PG, the vascular wall did not relax completely, i.e., spasm developed. This occurred usually after relatively large doses of PG, when the sensitivity of the smooth muscles to them was high, and when there was a tendency for the arterial walls to develop spasm. In response to repeated administration of PGA_1 and PGB_1, no regular change was found in the magnitude of their constrictor effects (Fig. 2). Consequently, PG may have a prolonged constrictor action on the arterial wall and may lead to the formation of continuous constriction of the spasm type. During the study of the mutual effect of PGA_1 and PGB_1, in some experiments they were found to be mutually potentiating.

After intraarterial injection of methysergide (0.1 mg), blocking serotonin receptors, and of phenoxybenzamine, tropaphen, dibenamine (1-2 mg of each), blocking α-adrenergic receptors, the effect of PG was not abolished. However, after intraarterial injection of reserpine (1-2 mg) the effect of PGA_1 and PGB_1 was reduced by more than 90%. This indicates that the effect of PG is somehow nevertheless connected with the same mechanisms as those through which serotonin and catecholamines act on smooth muscles.

From the standpoint of the development of arterial spasm, the effect of PG on the reactivity of the arterial wall relative to the vasoconstrictor action of other physiologically active substances is most interesting. After exposure to PGA_1 and PGB_1, the constrictor effects of serotonin and noradrenalin are regularly increased (Fig. 3). However, no increase in the effect of PG was observed under the influence of serotonin and noradrenalin.

The PG studied had no definite effect on the magnitude of the constrictor effects of an excess of K^+ or of ouabain, which is known to depend on depolarization of the plasma membranes of the smooth-muscle cells [6]. However, after temporary and considerable depolarization of the plasma membranes (produced by a five- to tenfold increase in the K^+ concentration in the perfusion fluid or by administration of 0.5-1 mg ouabain) the effects of PG were considerably reduced (by 67 ± 24 and 75 ± 25%, respectively, for PGA_1, and by 70 ± 9 and 73 ± 16% for PGB_1). Meanwhile, against the background of weak depolarization of the plasma membranes, the potentiating action of PG on the effects of serotonin and noradrenalin disappeared. All these observations could indicate that the effect of PG itself is connected with the function of the plasma membranes of smooth-muscle cells.

After removal of Ca^{2+} ions from the vessel wall (by prolonged perfusion of the artery with calcium-free Ringer–Krebs solution containing EDTA), the contractile action of PG on the smooth muscles of the arteries was reduced by 60-80% or actually completely abolished. Consequently, the action of PGA_1 and PGB_1, like that of other vasoconstrictor agents on the smooth muscles of the internal carotid artery [9], is effected through Ca^{2+}.

The possible role of PG in the mechanism of angiospasm is determined, first, by the special features of their constrictor effect (relatively long duration, absence of "habituation") and, second, by the fact that PGA_1 and PGB_1 change the reactivity of the smooth-muscle cells of the vessel wall in such a way that they develop a tendency toward prolonged, continuous contraction. This may facilitate the formation of angiospasm under conditions when other constrictor stimuli reach the artery, for example, the action of serotonin or normal nervous or humoral constrictor stimuli.

LITERATURE CITED

1. V. E. Anisimov, Yu. N. Kudryavtsev, R. M. Shakhirzayanova, et al., Ter. Arkh., No. 10, 119 (1974).
2. Kh. M. Markov, Usp. Fiziol. Nauk, No. 4, 98 (1970).
3. S. A. Mirzoyan, É. S. Gabrielyan, and É. A. Amroyan, Byull. Éksp. Biol. Med., No. 5, 75 (1975).
4. G. I. Mchedlishvili, The Function of the Vascular Mechanisms of the Brain [in Russian], Leningrad (1968).
5. G. I. Mchedlishvili, Pat. Fiziol., No. 2, 6 (1974).
6. G. I. Mchedlishvili, P. A. Kometiani, and L. G. Ormotsadze, Byull. Éksp. Biol. Med., No. 9, 19 (1972).
7. G. I. Mchedlishvili and L. G. Ormotsadze, Pat. Fiziol., No. 3, 72 (1970).
8. G. I. Mchedlishvili, L. G. Ormotsadze, and G. V. Amashukeli, Byull, Éksp. Biol. Med., No. 10, 3 (1967).
9. G. I. Mchedlishvili, L. G. Ormotsadze, and P. A. Kometiani, in: Current Problems in the Activity and Structure of the Central Nervous System [in Russian], Tbilisi (1976), p. 209.
10. G. S. Allen, L. M. Henderson, and S. N. Chou, J. Neurosurg., 40, 433 (1974).
11. J. Olesen, in: Blood Flow and Metabolism in the Brain (ed. by M. Harper et al.), Edinburgh (1975), pp. 4, 10.
12. C. D. Strong and D. F. Bohr, Am. J. Physiol., 213, 725 (1967).