EFFECT OF PROSTACYCLINE ON THE CEREBRAL VESSELS AND ITS PHARMACOLOGICAL MODULATION

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UDC 615.357.577.175.859].015.4:[612.184:612.824

KEY WORDS: prostacycline; cerebral vessels; contractility; drugs; atherosclerosis.

Prostacycline (PGI_2) is increasingly attracting the attention of research workers as an effective regulator of vascular tone, and it is recommended for use in clinical practice as a vasodilator agent for the pharmacological correction of regional circulatory disturbances [10]. There have been several investigations of the vascular effects of PGI_2, but many aspects of its influence on blood vessels (especially of the brain), remain unexplained. This applies to mechanisms of the vasodilator action of PGI_2 and their connection with the intimate processes regulating vascular tone. Special features of the vascular effects of PGI_2 in pathology, or especially in atherosclerosis, and also the effects of vasoactive drugs on them, have virtually not been studied. This state of affairs makes it difficult to assess the role of PGI_2 in processes of regulation of vascular tone and its changes in pathology.

In this paper we analyze the vasodilator action of PGI_2 on the cerebral arteries and its pharmacological modulation by certain drugs on intact and atherosclerotic vessels.

EXPERIMENTAL METHOD

Experiments were carried out on segments of human cerebral arteries removed from cadavers of persons dying from nonvascular diseases and from cerebral infarction, 2-6 h after death. Under these conditions the vessels are known to remain completely viable, to exhibit spontaneous activity, to respond normally to the action of vasotropic agents, and so on [1, 9]. During the investigation of vascular strips affected with atherosclerosis, preparations were taken from the basilar and middle cerebral arteries of persons dying from cerebral infarction. The strips were chosen so that atherosclerotic lesions occupied 25-35% of their area. Since the vascular preparations on which large and calcified plaques were present virtually did not contract, strips were taken on which the atherosclerotic lesions consisted mainly of thin plaques and lipid stains. The area of the latter was estimated by a direct planimetric method [4]. For comparison, some investigations on intact human vessels were duplicated on segments of rabbit carotid artery.

Contractility of spiral strips of blood vessels was recorded at 36°C on the HSE instrument ("Isotonische Élekt.;" West Germany) [6]. Ability of the agents tested to produce relaxation was estimated by the method in [5], with plotting of dose–effect curves. The relaxation produced in the presence of sodium nitrite (10^{-3} M) was taken as 100% relaxation of the vascular preparation. The results were subjected to statistical analysis by the nonparametric Wilcoxon–Mann–Whitney test.

EXPERIMENTAL RESULTS

In a concentration of 10^{-10}-10^{-7} PGI_2 effectively relaxed strips contracted by a depolarizing solution of K^+ (60 mM), by noradrenalin (10^{-6} M), $PGF_{2\alpha}$ (10^{-5} M), and serotonin ($5 \cdot 10^{-6}$ M). In high concentrations ($8 \cdot 10^{-6}$ M) PGI_2 itself induced contraction amounting to approximately 60% of the contraction induced by $PGF_{2\alpha}$. A similar picture was observed when the effect of PGI_2 on segments of the rabbit carotid artery was studied. These data are in agreement with those obtained by other workers [5].

The relaxing effect of PGI_2 was weaker on vascular strips from human arteries affected by atherosclerosis, the dose–effect curves were shifted to the right and became less steep,

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 102, No. 12, pp. 717-719, December, 1986. Original article submitted December 29, 1985.

0007-4888/86/0012-1715$12.50

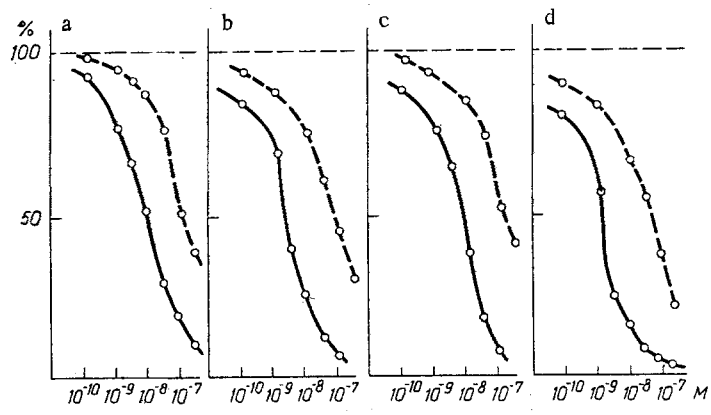

Fig. 1. Dose–effect curves for relaxing effect of PGI_2 on strips of human cerebral arteries contracted by depolarizing solution of K^+ (a), noradrenalin (b), $PGF_{2\alpha}$ (c), and serotonin (d) in experiment on intact (continuous lines) and atherosclerotic (broken line) vessels.

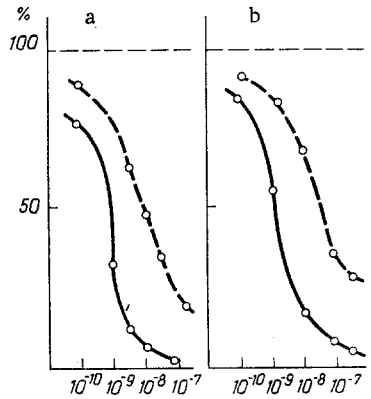

Fig. 2. Dose–effect curves for relaxing effect of PGI_2 on strips of human cerebral arteries contracted by $PGF_{2\alpha}$ against a background of nifedipine (a) and cavinton (b) in experiments on intact (continuous lines) and atherosclerotic (broken line) vessels.

and the maximal effect was not comparable with that obtained with sodium nitrite (Fig. 1). Conversely, the vasoconstrictor effect of high concentrations of PGI_2 was stronger on the atherosclerotic vessels and became comparable with the action of $PGF_{2\alpha}$.

To study how the relaxing effect of PGI_2 is modified by drugs, the action of two groups of preparations was tested: the calcium antagonist nifedipine (10^{-6} M) and the phosphodiesterase inhibitors cavinton ($5 \cdot 10^{-6}$ M) and dipyridamole ($8 \cdot 10^{-6}$ M). Nifedipine relaxes human cerebral arteries, previously contracted by $PGF_{2\alpha}$, by 20-40%, and against its background significant potentiation of the relaxing effect of PGI_2 was observed with a shift of the dose–effect curve to the left and lowering of EC_{50} (Table 1, Fig. 2). When the vascular preparations were treated with ouabain (10^{-4} M), a selective Na,K-ATPase inhibitor, the relaxing effect of PGI_2 was weakened on the control preparations and it was not potentiated against the background of nifedipine (Table 1).

To study interaction between PGI_2 and nifedipine at the level of intracellular Ca^{++} redistribution the effect of these agents was studied on tone of strips previously contracted by caffeine, which realizes its effect purely through release of Ca^{++} from intracellular depots [8]. It was found that under these conditions nifedipine had little effect on tone of the vascular preparations and potentiation of the vasodilator effect of PGI_2 due to its action was not observed (Table 1).

A different picture was observed when cavinton and dipyridamole were used. In both cases significant potentiation of the relaxing effect of PGI_2 was observed on strips contracted by

TABLE 1. Values of EC_{50} for Relaxing Effect of PGI_2 on Human Cerebral Arteries

Experimental conditions	Control	Nifedipine 10^{-6} M	Cavinton $5 \cdot 10^{-6}$ M	Dipyridamole $8 \cdot 10^{-6}$ M
$PGF_{2\alpha}$ (n = 11)	$8,5 \pm 0,6$ 10^{-9}	$7,5 \pm 1,1$* 10^{-10}	$1,3 \pm 0,25$* 10^{-9}	$2,9 \pm 0,5$* 10^{-9}
$PGF_{2\alpha}$ against the background of ouabain (n = 8)	$6,2 \pm 0,44$ 10^{-8}	$5,8 \pm 0,3$ 10^{-8}	$1,9 \pm 0,3$* 10^{-8}	—
Caffeine (n = 7)	$2,8 \pm 0,3$ 10^{-9}	$1,75 \pm 0,15$ 10^{-9}	$5,6 \pm 0,85$* 10^{-10}	$7,3 \pm 0,6$* 10^{-10}

Legend. n) Number of determinations. *P < 0.05 compared with control.

both $PGF_{2\alpha}$ and caffeine. Against the background of ouabain potentiation of the effect of PGI_2 by cavinton was still found, although it was rather weaker (Table 1).

The writers showed previously that the vasodilator effect of PGI_2 is mediated by two largely unconnected mechanisms: on one hand, by activation of Na,K-ATPase and intensification of Ca^{++} release through sodium-calcium exchange, and on the other hand, through an increase in the intracellular cAMP concentration and Ca^{++} reuptake into the intracellular depots [3].

The data given above show that calcium antagonists modify the vascular effects of PGI_2 at the level of its action on sarcolemmal Ca^{++} transport, which is due, at least partially, to Na,K-ATPase, and blocking of this component of the vascular effects of PGI_2 by ouabain leads to disappearance of the potentiating effect. Cavinton and dipyridamole, on the other hand, which inhibit phosphodiesterase, increase the ability of PGI_2 to raise the intracellular cAMP concentration, and the main role in their influence on the effects of PGI_2 displayed by processes of redistribution of intracellular Ca^{++}.

Interaction between the drugs tested with PGI_2 also was modified on the atherosclerotic vascular segments, for in the latter case the potentiating effect of nifedipine and cavinton became much weaker ($P < 0.05$) than in intact vessels (Fig. 2).

The vasodilator effect of PGI_2 and of the various drugs tested on atherosclerotic vessels is thus weakened. This may be the cause of development of the robbing syndrome when PGI_2 and the drugs studied in this investigation acted on the cerebral circulation. The reason why the effectiveness of PGI_2 and the potentiating action of drugs are reduced on vessels affected by atherosclerosis is an interesting question. Considering data given above on the role of Na,K-ATPase in the development of the vasodilator action of PGI_2 and on its interaction with pharmacological modulators, we studied the state of this enzyme in vascular preparations affected by atherosclerosis. Elucidation of this question was interesting also because weakening of Na,K-ATPase activity in atherosclerosis is characteristic of many biological structures [2].

Investigations of Na,K-ATPase activity, reflected in the degree of potassium relaxation [7], showed that potassium-induced relaxation of intact vessels was 44.0 ± 5.8%, but only 14.9 ± 4.0% ($P < 0.05$) on atherosclerotic vessels. This is evidence of inhibition of transport ATPase activity in atherosclerotic vessels, and this may be one cause of disturbances of the state of vascular tone in atherosclerosis and of changes in reactivity of the cerebral vessels to physiological and pharmacological agents under those conditions.

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ROLE OF KYNURENIN AND ITS DERIVATIVES IN CARDIAC ARRHYTHMIAS

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UDC 612.12-008.318-092:616-008.93:577.112.384.4]-092.9

KEY WORDS: kynurenin; kynurenin derivatives; cardiac rhythm.

Kynurenin is a natural derivative of the essential amino acid, tryptophan, and increased accumulation of kynurenin in the body, or its increased excretion, is regarded as a sensitive indicator of deficiency of pyrixodal-5-phosphate, i.e., the active form of vitamin B_6 [2, 3, 6]. No information could be found in the literature on the effect of kynurenin and its derivatives on the genesis of cardiac pathology. In patients with attacks of angina at rest, not responding to nitrites, kynurenin accumulation in the blood serum after administration of L-tryptophan is considerably increased [4]. Correction of intermediate tryptophan metabolism and normalization of kynurenin accumulation in the blood serum are accompanied by improvement of the patient's condition, or even by recovery [5].

The aim of this investigation was to study the effects of kynurenin and its derivatives on activity of the isolated frog heart.

EXPERIMENTAL METHOD

Experiments were carried out on 50 hearts isolated from winter frogs by Straub's method [1]. Activity of the isolated heart was maintained by Ringer's solution for cold-blooded animals, containing (in 1 liter): 6.5 NaCl, 0.3 g KCl, 0.002 g $CaCl_2$, and 0.2 g $NaHCO_3$. For the experiments various quantities of L-kynurenin sulfate (from Serva, West Germany), 3-hydroxy-DL-kynurenin (from Koch-Light, England), and kynurenic and xanthurenic (from Dr. T. Schuchardt, Munich, West Germany), 3-hydroxyanthranilic (Serva), and quinolinic acids (the last of these was synthesized in the Department of Organic Chemistry, J. Pelse Riga Polytechnical Institute, under the direction of Professor O. Ya. Neiland), were added to this solution. Cardiac contractions were recorded on a clockwork kymograph and an eight-channel polygraph (Nihon Kohden, Japan). Parallel with mechanical contractions, the electrical potentials of the heart were recorded on the polygraph; one electrode was located on the atrium, the other in the nutrient solution. The results were subjected to statistical analysis. Standard deviations of arithmetic mean values were calculated the t test carried out. The significance of results corresponding to the t test was calculated by the method in [8]. Differences were considered significant if their probability was over 95% ($P < 0.05$).

EXPERIMENTAL RESULTS

Under the influence of kynurenin the heart rate was slowed, but the slowing was significant only with L-kynurenin in a concentration of 10^{-4} M, when the heart rate (HR) reached 15.4 ± 0.9 beats/min, i.e., 29% less than initially. A further increase in the kynurenin concentration resulted in complete AV heart block (Fig. 1). Like kynurenin itself, 3-hydroxy-DL-kynurenin (Fig. 2) caused marked bradycardia which lasted 1-3 min. HR at this time was 10-40% below the initial value. The force of the cardiac contractions was unchanged. After addition of xanthurenic acid to the nutrient fluid in concentrations of 10^{-6} to 10^{-3} M, either transient bradycardia (for 15-60 sec) appeared, or prolonged bradycardia developed, with the heart rate falling by 10-30% below the initial level.

During short periods of bradycardia HR fell by 50% below the initial level. Bradycardia induced by xanthurenic acid was accompanied by weakening of the cardiac contractions by 5-10%.

Laboratory of Biochemistry, Latvian Research Institue of Cardiology, Ministry of Health of the Latvian SSR, Riga. (Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Val'dman.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 102, No. 12, pp. 719-721, December, 1986. Original article submitted February 19, 1986.

 0007-4888/86/0012-1718$12.50