Effect of Transitory Brain Ischemia on the Synthesis of Prostacyclin in Arterial Hypertension in Dogs

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Acute and chronic brain ischemia in dogs with rehabilitated hypertension is modeled by applying a tourniquet on the carotid artery. Occlusion of the coronary artery (60 and 120 min for 12 days) induces ischemic stress. Brain ischemia is accompanied by a decrease in plasma prostacyclin and the development of platelet hyperaggregation, which can produce thrombogenesis. The calcium antagonist nifedipine produces stress- and prostacyclin-protective effects by reducing platelet hyperaggregation and preventing thrombogenesis.

Key Words: *brain ischemia; prostacyclin; arterial hypertension; hypoxia*

Brain ischemia produced in rats by ligation of both carotid arteries induces dramatic inhibition of prostacyclin (PGI_2) synthesis in endotheliocytes of brain arteries [9]. Inhibition of PGI_2 synthesis in the aorta is less pronounced. Hypoxia modeled in a pressure chamber also led to inhibition of PGI_2 synthase activity of the aortic wall, which results in thrombophilia against the background of impaired protective platelet desaggregation [4]. In the present study we assessed the state of PGI_2 synthesis and its effect on platelet aggregation and desaggregation and on hemo- and cardiodynamics under conditions of transitory brain ischemia.

MATERIALS AND METHODS

Experiments were carried out on 8 dogs with rehabilitated arterial hypertension, i.e., normal blood pressure. For modeling sustained arterial hypertension both kidneys were twice ischemized using a rubber balloon. Yearly mountain adaptation at the Issyk Kul lake coast (1600 m) for 6-8 years results in adaptation of arterial hypertension. Blood pressure was measured by the S. N. Korotkov method on the carotid artery drawn into a skin flap by the Van Leerzum method. Acute transitory brain ischemia was modeled by ligation of the coronary artery in the skin flap for 60 and 120 min. Chronic transitory ischemia was modeled by daily 2-h ligation of the coronary artery during 12 days. Prostacyclin was measured as described elsewhere [3,5] using controlled 3-min occlusion of peripheral vessels in the hind paw of dogs with a rubber tourniquet (hypoxic stimulation of PGI_2 release from the vascular wall). The difference between the level of ADP-induced aggregation before and after occlusion was taken as the baseline blood level of PGI_2 [1,3,5]. When platelet aggregation after controlled occlusion surpassed that before occlusion (in % of total number of samples, 6 samples from each dog after addition of ADP), the case was considered to be an inadequate reciprocal platelet hyperactivation, a marker of platelet aggregate formation and thrombophilia. Mean dynamic arterial pressure, total peripheral resistance, neurocirculatory tone, and double product (DP) were measured as described previously [1,2,5]. Double product is an index of coronary reserve and myocardial oxygen demand (MOD), therefore MOD can be calculated from DP: $MOD=(DP_1-100)/(DP_2-x)$,

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where DP_1 and DP_2 are DP at rest (86 rel. units) and DP in stress and arterial hypertension (>86 rel. units). MOD>100 indicates myocardial hypoxia. DP positively correlates with the number of functional capillaries and negatively correlates with the number of closed (reserved) capillaries. The coronary reserve marker allows one to determine the number of functional and closed capillaries. At rest, the number of functional and closed capillaries constitutes 2300 and 2100 per mm^3, respectively (a total of 4400 per mm^3). The number of functional capillaries can be calculated from the following formula: $(DP_1—2300)/(DP_2—x)$, where DP_1=86 rel. units, while DP_2 is increased in stress and arterial hypertension due to reserve capillaries (the number of functional capillaries increases, while the number of reserve capillaries decreases). PGI_2 exerts coronarodilatating and coronaropreserving effects [6,7], which was determined by the formula $(PGI_2/DP)\times100$. The calcium antagonist nifedipine (Cordafen, 40 mg) was administered orally 30 min before the experiment. Blood pressure and heart rate were recorded immediately after removal of the ligature from the carotid artery and before the experiment.

RESULTS

The first session of acute transitory brain ischemia (60 min) resulted in a drop of blood PGI_2 level by 31.5% of the initial level (Table 1), while in dogs treated with nifedipine this parameter was less changed. After the second session (120 min) the decrease in PGI_2 blood content was more pronounced (by 37.1%). Calcium antagonist had a prostacyclin-protective effect: PGI_2 release surpassed its initial value by 27.3%. Chronic brain ischemia (12 days) reduced the blood content of PGI_2 by 42.8%. Under these conditions nifedipine also had a prostacyclin-protective effect: PGI_2 content surpassed its initial value by 29.5%.

Thus, calcium antagonist prevented the decrease in the content of PGI_2 both in acute and chronic brain ischemia. PGI_2-control of platelet aggregation in nifedipine-treated dogs was achieved via considerably reduced platelet aggregability (22.9 *vs.* 50.1% in the control) and enhanced desaggregation (41.1 *vs.* 0% in the control) in chronic brain ischemia.

Preservation of the liquid state of the blood through desaggregation of platelet aggregates and inhibition of thrombogenesis has an ameliorative effect on brain circulation in the course of prophylaxis of chronic brain ischemia with nifedipine (Table 1): coronarodilatory effect of PGI_2 in nifedipine-treated dogs was 31.1%, while in control animals it decreased to 12.8%. In acute ischemia (120 min), nifedipine potentiated the coronarodilatory effect of PGI_2 3.4-fold in comparison with the control.

Consequently, in acute and transient brain ischemia, calcium antagonist has a considerable coronaroprotective effect, which is an indicator of antithrombin-atherogenic status of the organism. Under conditions of chronic ischemia this parameter sharply decreases (more than 5-fold from the baseline) in control

TABLE 1. Content of Prostacyclin and Regulation of Platelet Aggregation and Desaggregation and Hemo- and Cardiodynamics in Control and Nifedipine-Treated Dogs with Acute and Chronic Brain Ischemia (*M±m*)

Parameters	Initial values	Acute brain ischemia				Chronic brain ischemia, 120 min for 12 days	
		60 min		120 min			
		control	nifedipine	control	nifedipine	control	nifedipine
Content of PGI_2, %	35.4±3	24±5	30.4±2	22.3±5	48.6±2*	20.0±3	49±3*
Difference in ADP-induced aggregation, %							
before occlusion	44±3	45±4	40.9±3	38±2	50.4±4	50.1±2	22.9±1**
after occlusion	28±3	37.1±1**	30.4±2	36±5	25.6±2*	41.5±4*	32.9±3
Reciprocal platelet hyperaggregation, %	6.6±0.5	16.6±3*	11.1±3	5.6±0.4	—	25±3*	83.3±6***
Coronarodilatory effects, %	34.4±2	12.9±2*	16.5±3*	12.8±1*	43.3±6	12.8±0.4*	31.1±6
Antithrombin-atherogenic state, rel. units	193.1±6	93.8±3*	135.7±5	164.8±5	135±4	30.3±2***	127±6
DP, rel. units	101±4	156±7**	181±9***	172±8***	111±5	156±7*	156±8*
MOD, %	17.4±2	81.9±5*	110±8**	100±6**	29±3	81.4±5**	81.4±6**
Number of functional capillaries per 1 mm	2701±19	4114±124	4400±0**	4400±0**	3000±71	2701±124	2701±128
Heart rate, beats/min	78±5	95±5*	117±3**	108±5*	74±3	95±6*	95±3*
Neurocirculatory tone, rel. units	0.9±0.01	1.2±0.3	1.3±0.4*	3.6±0.5***	1.8±0.3	—	1.8±0.6*

Note. *p<0.05, **p<0.01, ***p<0.001 compared with the initial level.

animals, and only 1.4-fold in nifedipine-treated animals (Table 1).

However, chronic ischemia is a severe cerebral pathology associated with overstrain of the coronary reserve, tachycardia, increased total peripheral resistance, sympathicotonia, and relapse of arterial hypertension (Table 1). DP is also a marker of MOD. This parameter is elevated in both groups of animals with transitory ischemia. Consequently, hypoxia of the myocardium in chronic brain ischemia is stable. Coronary reserve is to a great extent mobilized, which is confirmed by high DP. Previously closed coronary (reserved) capillaries are now opened (401 in the myocardium of each groups of dogs). Consequently, in chronic brain ischemia structural modifications of coronary reserve occur simultaneously in treated and nontreated dogs.

Prostacyclin due to its unique properties (thromboxane antagonist, antioxidant, membrane stabilizer, anti-ischemic factor, etc.) possesses cerebro- and cardioprotective activities [6,7].

Ischemia and hypoxia of the brain deplete PGI_2 reserves. It was shown in our laboratory that acute and chronic hypoxia (pressure chamber, 12,000 m) inhibits prostacyclin-synthetase activity of the aortic wall, while the calcium antagonist verapamil prevents this inhibition.

Thus, acute transitory and chronic brain ischemia damage endothelial cells of small and large blood vessels. Stress-induced release of catecholamines inhibits PGI_2 synthesis through activation of LPO and generation of free radicals [6,7]. Impaired PGI_2 control of platelet aggregation activity and reduced desaggregation result in thrombogenesis against the background of arterial hypertension relapse. Calcium antagonist reduces the aggregation ability of platelets by inhibiting calcium entry, thus converting prethrombosis into a less dangerous hemorrhagic state.

Thus, acute and chronic transitory ischemia are characterized by impaired prostacyclin regulation of platelet aggregation and desaggregation, primarily due to inhibition of prostacyclin synthesis in the endothelium. This results in enhanced platelet aggregation and weakened desaggregation. These shifts led to thrombogenesis (control), which can be effectively prevented with the calcium antagonist nifedipine. Preservation of the liquid state of the blood provides possibilities for maximum manifestation of the coronarodilating effect of PGI_2.

REFERENCES

1. M. A. Aliev, V. A. Lemeshenko, and A. K. Bekbolotova, *Kardiologiya*, No. 1, 64-65 (1993).
2. M. A. Aliev, V. A. Lemeshenko, and A. K. Bekbolotova, *Fiziologiya Cheloveka*, No. 6, 161-165 (1994).
3. V. P. Baluda, G. N. Sushkevich, and T. I. Lukoyanova, *Pat. Fiziol.*, No. 4, 80-82 (1980).
4. A. K. Bekbolotova, "Changes in ADP-induced and spontaneous platelet aggregation and antiaggregation (prostacyclin-dependent) activity of aorta wall during stress under conditions of medium and high altitudes," Author's Synopsis of Dissertation [in Russian], Frunze (1987).
5. A. K. Bekbolotova, V. A. Lemeshenko, and M. A. Aliev, *Byull. Eksp. Biol. Med.*, **115**, No. 6, 576-578 (1993).
6. Kh. M. Markov, *Pat. Fiziol.*, No. 6, 3-12 (1988).
7. Kh. M. Markov, *Kardiologiya*, No. 9, 5-11 (1989).
8. F. Z. Meerson, Adaptation, *Desadaptation, and Heart Failure* [in Russian], Moscow (1978).
9. N. N. Petrishchev, L. N. Shestakova, and E. V. Mel'nikov, *Fiziol. Zh.*, No. 11, 1515-1520 (1989).
10. V. P.-Reutov and S. N. Orlov, *Fiziologiya Cheloveka*, No. 1, 124-130 (1993).
11. A. P. Yurenev, Yu. S. Gerashchenko, and Yu. S. Dubov, *Ter. Arkh.*, No. 4, 9-10 (1994).