ТЕОРИИ, КОНЦЕПЦИИ, ГИПОТЕЗЫ...

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PROSTACYCLIN AS MEDIATOR OF HEMATO-VASAL INTERACTIONS

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Analysis of the phenomena of regional hemocirculation requires consideration of those multifold hemodynamic effects that develop in multifold result of a complex interaction between the vascular network and the blood it carries. To designate all the elements of this interaction we suggest the term of angiohaemic homeostasis that envisages permanent exchange of information between blood and the vessels, their response to various effects as a single system acting as a whole in the maintenance of blood supply to organs and tissues. A central place in these elements belongs, without doubt, to prostacyclin (PGI_2) whose high activity toward both the vessels and platelets is of a significant interest for scientists [1, 2]. It is likely that PGI_2 embodies in a greater extent the dualism of the nature of regulation of regional circulation, the essence of which lies in the parallel effect on vascular tension and blood suspensor stability. However, up to this day the analysis of the role of PGI_2 in the regulation of hematovasal interaction and regional hemocirculation is on the whole of a unilateral character. Practically only some aspects of its effects – vasodilative and antiaggregatory – are being investigated. Unilateral is also the investigation of PGI_2 participation in the pathogenesis of regional discirculation. Although, it is already clear that the disturbances in PGI_2 control of the vessel wall and platelet functional state is an important element in various by their character pathologic phenomena, including thrombosis, microembolic syndrome, atherogenesis, etc.[3, 4, 5]. The nature of these disturbances is merely explained by the decrease of PGI_2 synthesis in vessels. Speculations of this kind restrict the range of PGI_2 physiological role, do not permit to make a thorough analysis of its role as a universal mediator of hematovasal interaction. From this point of view the aim of our investigation was a more wide examination of PGI_2 role in the fold mechanisms that are responsible for the disturbance of its transmittery function in pathology.

Material and methods

Fresh citrate stabilized blood of healthy donors (53) was used in this investigation. Platelet aggregation was measured by the method of Born [6], using a two channel Payton aggregometer. The maximal extent of aggregation was estimated as a percentage of light transmission. Red cells aggregation was investigated by Kobatake et al. [7] and aggregation of polymorphonuclear leukocytes (PMNL) was estimated by the method of Fehr et al. [8].

The antiaggregatory activity of the rabbit central auricular artery was investigated by the method of Galli et al. in our modification [9, 10] (10 rabbits). The cranial end of the cervical sympathetic nerve was electrically stimulated (5 *Hz*, 7 *V*, 0.1 *msec*) in 20-30 *sec* interval by the electronic stimulator EST-7.

The influence of blood elements on the contractile activity of the vessel wall was investigated by the method of Gabrielian and Akopov [11].

Removal of endothelium was performed by the method of Samata et al. [12].

Influence of PGI_2 and Indometacin infusion on the constrictor reaction of cat cerebral vessels (12 cats) was performed by the stabilized autoperfusion method [13].

The change of the characteristics of PGI_2 stabilization-transformation was investigated in the blood of patients with cerebral atherosclerosis (25 patients) and healthy subjects (30) by the whole-blood aggregometer (Chrono-Log).

The values were expressed as mean ±SE. Differences between means were analyzed by the Kruscal-Wallis test (non parametric analysis of variance (ANOVA). Identification of homogeneous groups (cluster) of cases was performed using cluster analysis followed by discriminant analysis. The power of the factor influence was calculated using ANOVA. All calculations were made using SPSS PC+statistical software [14].

Results and discussion

As it has been mentioned above, analysis of PGI_2 effect on blood is limited by the analysis of its effect on platelets. Indeed, Table 1 shows that PGI_2 abruptly inhibits platelet aggregation under various inductors, causing at the same time decay of already generated aggregates, though on a somewhat higher concentration. But besides the effect on platelets, this agent influences also the aggregation of other blood elements. As it is seen from Table I, it also hinders erythrocyte aggregation, that can be ascribed to the modifying effect of PGI_2 on the conformation of erythrocyte membranes [15]. Finally, the PGI_2 blocks the aggregation of polymorphonuclear leukocytes induced by a chemotactic agent (FMLP). This is in conformity with the recently observed capacity of eicosanoids to interfere in the metabolism of PMNL with the inhibition of the metabolic outburst characteristic of their activation [16].

Thus, the role of PGI_2 in the regulation of blood suspensor stability is not limited by the platelets only but extends to other cells as well, stress-

ing the universal role of PGI_2 as a factor inhibiting the development of rheologic disturbances.

Table 1

Effect of PGI_2 on human blood cell aggregation

Type of cell	Inductor of aggregation	ED_{50} for PGI_2 effect, *mg/m*
Aggregation in platelet rich plasma (PRP) (n=10)	ADP	1.65±0.21
	Collagen	2.80±0.23
	Epinephrine	0.83±0.04
	Arachidonic Acid	3.40±0.31
	Thrombin	15.20±3.00
Desaggregatory effect in PRP (n=10)	ADP	7.80±0.90
	Collagen	19.40±2.10
Erythrocyte aggregation (n=12)	Gamma globulin + Fibrinogen	1267.20±97.60
PMNL aggregation (n=9)	FMLP	147.60±29.40

Hence it follows that PGI_2 can mediate modifying effect on the hematovasal relations of various physiological factors. For some of these factors the capacity to influence PGI_2 generation in the vessels is found, but the analysis of their effect is carried out only "from blood". It is supposed, that on PGI_2 synthesis influence compounds present in plasma and directly contacting with the endothelium. In addition to this we studied the possibility of an analogous effect of a part of the nervous contour of circulation regulation, namely its adrenergic component. On the model of rabbit isolated circulatory perfused auricular artery the effect of sympathetic stimulation on the antiaggregatory activity of its wall was investigated. The phenomenon of an absolute disappearance of vessel antiaggregatory activity under sympathetic stimulation was revealed (Table 2). Consequently, PGI_2 becomes involved in feedback relations of adrenergic transmission mediating the effect of sympathetic nervous system on blood rheologic capacity and aggregatory state.

Table 2

Antiaggregatory effect of rabbit central auricular artery before and under stimulation of sympathetic cervical nerve

Condition	Inductor of aggregation	Aggregation in PRP before infusion (%)	Aggregation in PRP after infusion (%)
Control	ADP 10^{-4}M	50.9	34.7*
Sympathetic stimulation		52.2	57.1
Control	Collagen 2	38.1	7.0*
Sympathetic stimulation	mkg/ml	64.9	62.6

* $P<0.05$

This enlarges the perception of the ways of influence of sympathetic nervous system on the regional hemocirculation, and shows that the development of dishaemia induced by it may be associated with not only vasomotor but also "hematogenic" disturbances of terminal perfusion.

Generally PGI_2 is considered as a factor mediating the effect of vessel wall on the circulated blood. However not less interest represents the analysis of its role in the development of polar effects, first of all associated with the change of vascular tension. On a homeostatized perfused vascular segment (cat carotid artery and human middle cerebral artery) it was shown that collagen-activated platelets activated with FMLP PMNL, while introduced to the perfusion canal, bring forth contraction of vascular segment, the degree and duration of the contraction increasing 1.5-2 times after the removal of the endothelium.

When the deendothelized vessel is perfused by a solution with minimal PGI_2 concentration, the contracting effect of both the platelets and PMNL sufficiently decreases (Table 3). In a higher degree this phenomenon is observed in case of combining PGI_2 with the calcium antagonists, e.g. Nifedipin.

This is, probably, connected with mutually complementary mechanisms of the vasodilatative effect of these agents: while Nifedipin hinders calcium supply to the smooth muscle, PGI_2 acts as a factor that can limit, if not prevent, the development of an angiospasm caused by the disturbance of the equilibrium between blood and vessel wall [16]. Analogous function of calcium antagonists as agents of regional discirculation therapy may lie in the positive interaction with PGI_2.

Table 3

Influence of PGI_2 and Nifedipine on the spasmogenic effect of activated human platelets and PMNL

		Suppression of vasoconstrictory effect (%)	
		Platelets	PMNL
PGI_2	10^{-9} *M*	76.2±6.0*	54.6±6.0*
	10^{-10} *M*	23.6±3.9*	15.7±4.3
Nifedipin	$5x10^{-6}$ *M*	85.1±5.7*	62.1±5.6*
	$5x10^{-8}$ *M*	26.8±3.9*	23.6±4.1*
PGI_2+Nifedipin	10^{-10} *M* + $5x10^{-8}$ *M*	83.6±3.4*	79.6±8.0*

**P<0.05*

Direct investigations of the effect of activated platelets and PMNL on PGI_2 synthesis in the vessel wall by the change of level of its stable metabolite – 6-keto-PGF1 alpha-estimated by means of radioimmunoassay revealed that after a 3 minute contact with collagen-activated platelet suspension, its level increases to 42.5±7.9% with the suspension of activated PMNL – to 67.4±9.3%. Consequently, PGI_2 is able to form

feedback relations that will delimit the development of an angiospasm. It was observed that vascular segments with removed endothelium lose their capacity to develop such a reaction in response to the effect of blood cells, although basal PGI_2 level in them might not change. This means that pools of PGI_2 synthesized in various layers of vessel wall differ functionally, and its reactive fraction is PGI_2 generated in the very endothelium.

However, the role of PGI_2 as an antispasmatic agent is not limited by the reaction of the "hematogenic" component of the pathogenesis of vasospasm but involves its other elements also. In the investigation of the cerebral vessel resistance by the method of brain autoperfusion, the role of PGI_2 in the regulation of adrenergic influence on vascular tension was analyzed.

It appeared that infusion of PGI_2 in a concentration in which PGI_2 itself has very slight effect on the vascular tension, abruptly inhibits constrictory reaction of cerebral vessels after the introduction of noradrenalin and sympathetic stimulation.

An exactly opposite pattern is observed in case of PGI_2 synthesis inhibition in cerebral vessels by the infusion of Indometacin (Table 4).

Constrictory effect in the control is taken as 100%; the measure of the constrictory effect was the change of perfusion pressure.

Consequently, PGI_2 is an agent, which effectively modifies different by nature effects on vascular tension, acting as a mediator in the system of feedback relations, limiting the danger of its abrupt changes.

Table 4

Influence of PGI_2 (50 *mg/kg/min*) and Indometacin (1 *mg/kg/min*) infusion on the constrictory reaction of cat cerebral vessels induced by Noradrenalin and sympathetic stimulation (n=10)

Type of stimulation	Control	On the background of PGI_2 infusion	On the background of Indometacin infusion
Noradrenalin 5 *mg/kg i/c*	100	55.1±12.3*	125.2±9.4*
Sympathetic stimulation 5 *Hz*, 7 *V*, 0.5 *min*	100	6.9 ± 4.7	281.4±26.1*

*$P<0,05$

The above said and the data of other researchers bring to the conviction that PGI_2 may be considered as a multiprofile regulator of the functional state of blood elements and vessels and their interaction, as well as a modulator of neurohumoral influence on the system blood-vessel wall. Correspondingly, considerable interest represent the questions: in what cases a decrease of the level and efficiency of its hematovasal influence can be expected, and what is the role of these changes in the pathogenesis of regional dyshaemia?

Table 5

Change of the characteristics of PGI_2 stabilization-transformation in the blood of patients with cerebral atherosclerosis

Investigated Parameter	Parameters variation (n=30)	Healthy subjects (n=25)	Patients with atherosclerosis
Degree of PGI_2 physiological activity lengthening in the presence of plasma	>3.0	10(33)	3(12)
	1.5-3.0	17(57)	6(24)
	<1.5	3(10)	16(64)
Degree of PGI_2 physiological activity shortening in the presence of platelet suspension	>5.5	4(13)	- (0)
	3.5-5.5	15(50)	4(16)
	1.5-3.5	8(27)	9(36)
	<1.5	3(10)	12(48)
Degree of PGI_2 physiological activity shortening in the presence of erythrocytes	<1.25	19(63)	2(8)
	1.75-1.25	8(27)	6(24)
	1.75-2.5	3(10)	17(68)
Level of PGI_2 antiaggregatory activity decrease in whole blood after 16 min of incubation in % from the initial value	<10	9(30)	2(8)
	10-35	15(50)	4(16)
	35-60	6(20)	10(40)
	>60	- (0)	9(36)

Number of patients as a% is given in parenthesis

Certainly alteration of PGI_2 synthesis level in the vessel wall and some other tissues is of considerable importance, but is the modification of its function in pathology limited by this? In our studies we performed the analysis of another ring ensuring the thoroughness of PGI_2 hematovasal effects, that may also be responsible for their changes in pathology. It is known that the time of the active presence of PGI_2 in the blood flow, and hence the markedness of its physiological effects, is to a greater extent connected with the capacity of plasma proteins, first of all albumin, to stabilize this agent, and that of the erythrocytes, on the contrary, to decay it [9, 10]. On the other hand, during the interaction with the platelets PGI_2 turns into a stable active metabolite - 6-keto-PGF1 alpha [3]. In the complex interaction of these processes is determined the problem of those concrete characteristics which will define the destiny of PGI_2 after the release from the vessel in the course of its passage to the executive receptors of target cells. Earlier we have devised a complex of methods of biological testing of the process of PGI_2 stabilization-transformation in blood, suitable for their investigation in human beings [9, 3]. Table 5 gives the data on the change of the characteristics of these processes in patients with atherosclerosis with prevailingly impaired cerebral vessels. It is obvious that in patients with atherosclerosis, as compared with healthy subjects, the processes of PGI_2 stabilization-transformation are significantly disturbed expressed, by the shortening of the time of its active presence in blood flow. Here of certain importance is the fact that in various patients maximal disturbance of these processes

occurs in various links: in some of the patients it is the abrupt increase of PGI_2 decay by erythrocytes, in others – an almost total disappearance of plasma stabilizing activity, etc. To assess the resultant of all the elements responsible for the prolongation of PGI_2 physiological activity, estimation of the dynamics of the alteration of its antiaggregatory effect in whole blood is suggested (Table 5). The level of its decrease will be the resultant from the prolonging effects of PGI_2 influence of albumin and platelets and the contrary influence of erythrocytes. However, it is not excluded that there exist in blood other factors, also influencing this process. As seen from Table 5, high percentage constitute patients with a quicker decay of PGI_2. However it should be considered that factors bringing to this phenomenon differ in various patients, consequently different are also objects to which should be directed corresponding corrective influence. It is also important to note that in a number of patients disturbance in one of the links of transformation-stabilization process might be practically compensated in another link. For instance, an abruptly increased PGI_2 decay by erythrocytes was parallel with a very high stabilizing capacity of plasma or vice versa. In any case it is clear that during atherosclerosis there takes place a complex and strictly individual process of PGI_2 transformation-stabilization disturbance, which through different means brings to the decrease of the efficiency of its hematovasal influence. Along with the decrease of PGI_2 generation level, it will condition the insufficiency of PGI_2 control of hemato-vasal relations in pathology. On the other hand, disturbance of stabilization-transformation processes may be closely related to the possibility of using PGI_2 as a drug. Naturally, if the injected PGI_2 is decayed very quickly, then it requires consideration of its dosage, manner of injection, etc.

However, even in the phase of the realization of PGI_2 effect on the elements of the system blood-vessel wall, first of all the vessels and platelets, there may be observed in pathology significant shifts from the normal level. This is a rather complex and insufficiently investigated problem; however it is already clear that PGI_2 final effect depends upon a whole series of matters. One of them is the character of the influence leading to an alteration in platelet or vessel functional status as development of aggregate generation or a spasm. In ordinary investigations analysis of PGI_2 vascular-platelet effects is carried out through influencing the vessels by one of the vasoconstrictive agents, or in the presence of a definite inductor of platelet aggregation. But in real conditions and especially in pathology, more probable is the situation when vessel or platelet dysfunction is caused by a complex combination of such agents.

Analysis of the peculiarities of PGI_2 effect on vessels was carried out on the section material of persons deceased from cerebral infarction: PGI_2 effect was compared on standardized segments of middle cerebral arteries obtained from the focus of infarction and from the contralateral hemisphere in the first 2-3 *h* after death. It appeared that ED50 for the first category of vessels equaled $9.7\pm3.7\times10^{-9}M$, for the second – $3.5\pm0.9\times10^{-9}M$; for some pairs of vessels the difference being over several

orders. Thus, in patients with cerebral vessel pathology signs of alteration of platelet and vessel basal sensitivity toward PGI_2 can be revealed. It is not excluded that the decrease of the efficiency of its vascular-platelet effects will appear as an important cause of the development of discirculation, and those vascular which lose their sensitivity toward its vasodilator influence to a greater extent will be the highest risk zones for its localization.

The results of the last years investigations suggested that endothelial-dependent relaxation of vascular smooth muscle reflects the release of more than one factor. In vascular endothelium NO, a mechanism sensitive to the extravascular K^+ concentration, contribute approximately equally a prostanoide-mediated mechanism to the relaxation [17, 18, 19, 20]. The direct evidence of this suggestion is the demonstration of release of PGI_2 in the vascular endothelium through NO as a primary signal for relaxation [19].

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ՊՐՈՍՏԱՑԻԿԼԻՆԸ ՈՐՊԵՍ ԱՐՅՈՒՆ-ԱՆՈԹԱՅԻՆ ՓՈԽԱԶԴԵՑՈՒԹՅՈՒՆՆԵՐԻ ՄԻՋՆՈՐԴԱՆՅՈՒԹ

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Կատարված հետազոտությունները վկայում են, որ պրոստացիկլինը (PGI-2) ընկճում է զանազան մակածիչների ազդեցության հետեւանքով խթանված մարդու արյան թիթեղիկների, էրիթրոցիտների եւ բազմաձեւ-կորիզավոր լեյկոցիտների ագրեգացիան: Ճագարի ականջի մեկուսացված զարկերակի վրա կատարված ուսումնասիրությունները ցույց են տալիս, որ սիմպաթիկ նյարդի էլեկտրակոս խթանումը առաջացնում է անոթի պատի հակաագրեգացիոն հատկության ընկճում (ADP-ի համար 31.8%, իսկ Collagen-ի համար՝ 81.6%): Պրոստացիկլինը ընկճում է նաեւ ուղեղի զարկերակների կծկելիությունը:

Քնային եւ ուղեղային միջին զարկերակների էնդոթելազերծված հատվածների վրա կատարված ուսումնասիրությունները ցույց են տալիս, որ արյան ակտիվացրած թիթեղիկները եւ բազմաձեւ կորիզավոր լեյկոցիտները առաջացնում են անոթների մկանաթելերի ջղակծկումներ, որոնք ուժեղանում են էնդոթելազերծման պայմաններում: Այս ռեակցիաները ընկճվում են պրոստացիկլինի եւ նիֆեդիպինի ազդեցության պայմաններում: Բացահայտված է նաեւ, որ արյան ակտիվացրած թիթեղիկները եւ բազմաձեւ-կորիզավոր լեյկոցիտները խթանում են պրոստացիկլինի սինթեզը անոթի պատում: Ստացված տվյալները վկայում են արյուն-անոթային փոխհարաբերություններում պրոստացիկլինի կարեւոր դերի մասին:

ПРОСТАЦИКЛИН КАК МЕДИАТОР ГЕМАТОВАЗАЛЬНЫХ ВЗАИМОДЕЙСТВИЙ

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Исследована роль простациклина (ПГИ2) в регуляции гематоваскальных взаимодействий. Установлено, что ПГИ2 угнетает агрегацию тромбоцитов, эритроцитов и полиморфно-ядерных лейкоцитов (ПМЯЛ) в крови человека, вызванную рядом индукторов. На модели циркуляторно-изолированной перфузируемой ушной артерии кролика

установлено, что в условиях симпатической стимуляции исчезает антиагрегационная активность сосудов. Наблюдается также подавление сократительной реакции мозговых сосудов кошек под влиянием инфузии ПГИ2. На перфузируемых сосудистых сегментах сонной артерии кошек и среднемозговой артерии человека показано, что активированные тромбоциты и ПМЯЛ вызывают сокращение сосуда, усиливающееся в условиях деэндотелизации, а ПГИ2 и нифедипин угнетают его. Установлено, что после контакта с активированными тромбоцитами и ПМЯЛ возрастает синтез ПГИ2 в стенке сосудов. Полученные результаты свидетельствуют о роли ПГИ2 как универсального медиатора гематоваскальных взаимодействий.

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