Role of Prostaglandin E_2 in Neurohumoral Regulation of the Cardiovascular System

V. I. Savchuk, Z. A. Nechaeva, and A. Yu. Runikhin

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The role of prostaglandin E in neurohumoral regulation of visceral functions is studied. Prostaglandin E_2 modulates cholinergic reflex reactions of the cardiovascular system and activates cardiovascular receptors related to unmyelinated fibers of the bulbar afferent system. The depressor effects of prostaglandin E_2 are fully expressed only when bulbar cardiovascular innervation is preserved.

Key Words: *cholinergic; modulatory; selective*

Classical concepts on vegetative regulation of the cardiovascular system are now revised on the basis of accumulating data on modulation of these processes by endogenous bioactive substances constantly synthesized in the organism. Numerous investigations demonstrate that these substances modulate the state of sympathetic and parasympathetic regulation and functional activity of these systems, thereby modifying the intensity and sometimes the nature of reflex reactions effected through the well-known mechanisms of vegetative regulation [4,6,8,10]. It has been shown that this modulation of vegetative regulations can be accomplished on the pre- and postsynaptic levels due to modulation of transmitter processes [5,8,10,11].

Such a modulation becomes even more important under pathological conditions [1-3]. It is known that stress, ischemia, and hypoxia activate synthesis of prostaglandins (PG) which diminish the effects of catecholamines by modulating adrenergic regulatory mechanisms. This leads to adaptation of the systems to pathological conditions. It has been shown that apart from adrenergic regulation, PG can also modulate cholinergic reactions of the intestinal and cardiovascular system [3,9]. The nature and intensity of modulatory effect of PG on cholinergic reactions depend on the state and activity of the sympathoadrenal system. Under certain conditions epinephrine activates the parasympathetic nervous system through enhanced PG synthesis and increased content of choline [11].

The aim of the present study was to investigate the modulatory effects of PGE_2 on cholinergic reflex reactions in the cardiovascular system.

MATERIALS AND METHODS

Acute experiments were performed on 98 cats weighing 2.5-3 kg narcotized with Nembutal (40 mg/kg) and artificially ventilated with constant control of blood gases and pH. A PGE_2 bolus was injected into the left auricle. For evaluation of PGE_2 effects the following parameters were measured: arterial pressure, maximum systolic and diastolic pressure in the left ventricle, the rate of left ventricular pressure development and its first derivative, rate of relaxation, ECG, heart rate, and activity of afferent fibers of the right vagus nerve. Selective thermal blockage of myelinated (A) and unmyelinated (C) afferent fibers was performed for differential evaluation of the role of A- and C-afferent bulbar structures in realization of PGE_2 effects. All parameters were recorded on a Mingograf-82 device. The data were processed by the Student's t test.

RESULTS

Injection of PGE_2 (50 μg/kg) into the left auricle of intact animals with preserved bulbar innervation produced a 10-30-sec depressor effect which attained the

Russian State Medical University; Cardiology Research Center, Russian Academy of Medical Sciences, Moscow

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TABLE 1. Hemodynamic Parameters (Δ%) Characterizing Depressor Effect of PGE_2

Intervention	Arterial pressure		Maximum pressure in left ventricle	Rate of left ventricle pressure development, dP/dt_c	Rate of relaxation, dP/dt_r	Heart rate, beats/min
	systemic	mean				
Intact animals	56.4±4.8***	46.7±4.6**	44.0±5.5***	55.5±8.7**	57.0±12.5*	
Bilateral vagotomy	36.2±4.4***	27.6±3.8**	28.1±6.4***	43.0±2.3***	50.0±4.5***	
Stimulation of vagus nerve:						
before PGE_2		18.5±2.7	12.6±1.8	16.4±1.7	13.5±1.6	41.3±3.9
against the background of PGE_2		35.9±3.2***	15.6±1.3**	19.1±1.7**	33.1±2.4**	53.8±4.3***
PGE_2 effect:						
after left vagotomy		42.1±2.4***	34.2±4.1**	38.6±1.2**	48.3±3.1***	
cooling of the right vagus to 8°C		40.3±3.8**	32.7±3.3**	35.0±6.6**	41.7±8.5**	
cooling of the right vagus to 2°C		24.3±2.6**	20.5±3.6**	14.4±1.1***	15.0±0.2*	

Note. *$p<0.05$, **$p<0.01$, ***$p<0.001$ compared with initial values (before PGE_2).

maximum 60-70 sec postinjection. This was characterized by a drop in systemic arterial pressure and maximum systolic pressure in the left ventricle, and the rate of left ventricular pressure development (dP/dt_c) and relaxation (dP/dt_r) (Table 1). This depressor effect develops by a complex mechanism. On the one hand, it results from direct influence of PGE_2 on vascular smooth muscles and cardiomyocytes [1,7], but on the other, it is mediated through PGE_2-induced modulation of the cholinergic system. Although the nervous mechanism has been observed in a number of investigation [3,12], its role in realization of the depressor effect of PGE_2 is poorly understood and practically underestimated.

For evaluation of the role of cholinergic system in realization of the depressor effect of PGE_2 additional special experiments were carried out. In series 1, PGE_2 was injected to vagotomized animals. In series 2, electric stimulation of the vagus nerve was performed against the background of PGE_2 injection. After bilateral vagotomy (series 1), the depressor effect produced by 50 μg/kg PGE_2 was much weaker than in intact animals with preserved bulbar innervation, i.e., PGE induced less pronounced changes in all hemodynamic parameters (arterial pressure, maximum pressure in the left ventricle, rate of left ventricular pressure development, and rate of relaxation (Table 1). This attests to an important role of the bulbar afferent system in realization of the depressor effect of PGE_2. These findings suggest that this effect is realized not only through direct influence of PGE_2 on vascular smooth muscle cells and cardiomyocytes but also through indirect influence on the cholinergic system.

The involvement of cholinergic component into realization of the depressor effect of PGE_2 was confirmed in series 2. PGE_2 pretreatment modulated ino- and chronotropic reaction caused by electric stimulation of the vagus nerve. In these experiments the left vagus nerve was cut and the right vagus was stimulated for 5 sec with electric pulses (5 V, 1 msec). Changes in the studied hemodynamic parameters caused by electric stimulation of PGE_2-treated and intact animals (n=23) were compared.

Stimulation of the right vagus nerve led to a drop in the mean arterial pressure, maximum pressure in the left ventricle, and the rate of left ventricular pressure development, rate of relaxation, and heart rate (Table 1). In PGE_2-treated animals, stimulation of the right vagus nerve with pulses of the same intensity produced more pronounced changes in all hemodynamic parameters (Table 1). We believe that these potentiating effect of PGE_2 results from a PGE_2-induced increase in the epinephrine release and reflects its modulatory influence on classical synaptic processes.

It has been previously shown that the modulatory effects of PGE_2 on reflex processes can be mediated through different mechanisms. Our results suggest that primary activation of chemosensitive and chemoreceptor bulbar cardiovascular afferent fibers, which are primarily presented by unmyelinated C-fibers, is an important component in the formation of the modulatory effect of PGE_2 on cholinergic reaction of the cardiovascular system. This conclusion was made on the basis of experiments where the depressor effects of PGE_2 were reproduced against the background of selective thermal blockage of A- and/or C-fibers of the right vagus nerve (n=20) (the left vagus nerve was preliminary cut). Table 1 shows that cooling of the right vagus to 8°C that produces a selective block of myelinated afferent A-fibers had

no effect on the magnitude of the depressor effect of PGE_2 (50 μg/kg). This implies that myelinated cardiovascular fibers of the vagus nerve do not participate in the realization of the depressor effect of PGE_2, which was confirmed by direct measurements of bioelectric activity of cardiac mechanoreceptors before and after PGE_2 injection.

In experiments with complete thermal blockage of A- and C-afferent fibers of the right vagus (cooling to 2°C) after preliminary left vagotomy, the intensity of the depressor effect of PGE_2 was considerably decreased (Table 1).

Data obtained in experiments with selective thermal blockage of afferent bulbar fibers of the vagus nerve suggest that the reflex component of the depressor effect of PGE_2 is a result of activation of the receptors related to unmyelinated C-afferent cardiovascular fibers of the vagus nerve.

All these findings suggest that apart from well-known direct influence on the vascular smooth muscles and cardiomyocytes, PGE_2 activates cardiovascular receptors coupled with unmyelinated fibers of the bulbar afferent system. The depressor effects of PGE_2 are fully expressed only if the bulbar cardiovascular innervation is preserved. On the other hand, PGE_2 modulates cholinergic reflex reactions of the cardiovascular system. These findings agree with the observation that PG stimulate vascular chemosensitive receptors coupled with C-afferent fibers in the lungs and respiratory tract [6,7] and modulate cholinergic reactions of the gastrointestinal tract [9].

The above data provide the basis for the concept of complex multiloop neurohumoral regulation of visceral functions and an important role of PG in this regulation. Under pathological conditions the modulatory effect of PG on reflex reaction can be changed considerably.

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