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On the Possible Mechanism of Elevation of the Arterial Wall Extensibility in Response to Norepinephrine.

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Abstract

It is known that intravenous infusion of norepinephrine (NE) into anaesthetized animals is associated with an increase of arterial vascular extensibility simultaneous with a reduction of its hydraulic conductivity. One possible explanation of NE ability to enhance vascular extensibility is an activation of endothelial alpha2-adrenoceptors by catecholamines and nitric oxide (NO) release, since NO has this ability. The results of the present study provide an evidence for a synergetic regulatory role of NO in this activity with release of NO stimulated by norepinephrine.

We investigated a role of NO in regulation of arterial vascular responses to volumetric blood flow rate changes with intravenous NE infusion. The experiments were carried out on cats anaesthetized with urethane and sodium oxybutirate and subsequent myorelaxation and mechanical ventilation. The arterial pressure was recorded in the left carotid artery by an electronic manometer. Then the laparotomy was made and the hindquarter vascular region was autoperfused with variable flow pump.

In the experiments we performed incremental changes of volumetric perfusion rate such a way that perfusion pressure values at the entrance of a perfused vascular region was 50-250 mm Hg. We performed uniform changes of volumetric perfusion rate before and after administration of drugs and then plotted a «blood flow-pressure» relationship. Then we calculated index of vascular extensibility, index of arterial pressure stability and hydraulic resistance by variation of volumetric perfusion rate.

We estimated the effects of intravenous angiotensinamide (AA) infusion at a dosage of 15 mkg/kg/min and NE infusion at a dosage of 10 mkg/kg/min in intact animals. NE infusion was also performed on the background of preinhibition of nitric oxide synthase by intravenous NG-nitro-L-arginine (L-NAME) at a dosage of 10 mg/kg.

AA infusion resulted in an increase of hydraulic arterial resistance, decreases of extensibility and arterial pressure stability in intact animals. NE infusion resulted in an increase of hydraulic arterial resistance associated with increase of its extensibility. The arterial pressure stability remained unchanged.

NE infusion on the background of L-NAME resulted in significant decrease of vascular extensibility and pressure stability on the background of total vasoconstriction.

These results suggest that an increase in NO release contributes to the increase in vascular extensibility induced by NE in animals with intact endothelium.

INTRODUCTION

It is known that intravenous infusion of norepinephrine (NE) into anaesthetized animals is accompanied by an increase in the arterial vascular extensibility simultaneous with a reduction of its hydraulic conductivity [3]. One possible explanation of NE's ability to enhance vascular extensibility is an activation of endothelial alpha2-adrenoceptors by catecholamines and nitric oxide (NO) release [5,6,8], since NO has this ability [2]. The results of the present study provide evidence for a synergistic regulatory role of NO in this activity with release of NO stimulated by norepinephrine.

METHODS

The experiments were carried out on 22 cats (2.5-4 kg weight) anaesthetized with an intraperitonal injection of urethane (800 mg/kg) and sodium oxybutirate (800 mg/kg) and subsequent curarization and mechanical ventilation. Autoperfusion of hindquarter vascular region was performed to plot a «blood flow-pressure» relationship at incremental changes of volumetric perfusion rate [1,3] in all of the experiments. The following parameters were recorded: arterial pressure (AP) in the carotid artery, heart rate (HR), and perfusion pressure (PP) at the entrance of perfused vascular region. By using the «blood flow-pressure» relationship, we estimated the size of the PP increase in response to the uniform perfusion volume increase before and after NE infusion, changes of hydraulic vascular resistance, and the index of vascular extensibility using current methods [1]. The principle of this method is as follows. On the basis of a mathematical model of type

$$Q=Q0/\mathit{gamma}\,(1-e[-\mathit{gamma}\cdot \mathrm{deltaP}/P0]),$$

where P and Q are PP and volumetric perfusion rate, P0 and Q0 are scale factors having dimensions of pressure and blood flow, respectively; the index *gamma* reflecting the degree of correspondence between vascular properties and linear hydraulic conductor properties. This correspondence was observed at $\mathit{gamma} = 0$, $\mathit{gamma} < 0$ provides evidence for reduction, and $\mathit{gamma} > 0$ does so for an increase in the hydraulic vascular resistance with increase in simultaneous perfusion volume. Thus, the comparison of *gamma*-indices before and after injection of the drug allows estimating a dilatation (or constriction) of perfused vessels at the same change of perfusion volume.

PP increase recorded simultaneously reflects total ability of arterial vessels to stabilize transmural pressure in response to changes of volumetric blood flow rate.

In 9 experiments comprising the first series of the study all of the parameters were estimated before and during 60-min intravenous NE infusion at a dosage of 10 mkg/kg/min. In 6 experiments, i. e. the second series of the study, the NO synthesis inhibitor NG-nitro-L-arginine methyl ester was administered at a dosage of 10 mg/kg to cats before NE infusion. In 7 experiments, i. e. the third series of the study, animals underwent an intravenous angiotensinamide infusion (AA) at a dosage of 15 mkg/kg/min at 15 min.

The statistical estimates were performed with use of paired and unilateral Student's test: statistical significance was defined as $p < 0.05$.

RESULTS AND DISCUSSION

In the first series, the anaesthetized cats had the initial mean AP 117 +/- 5 mm Hg and HR 186 +/- 8 beats/min. PP was 72 +/- 7 mm Hg at the minimal volumetric perfusion rate of 16 +/- 2 ml/min. Increasing the perfusion volume to 58 +/- 4 ml/min resulted in PP increase to 177 +/- 13 mm Hg. PP increase was accompanied by decrease of hydraulic vascular resistance (from 47 +/- 0.5 to 3.1 +/- 0.2 mm Hg/ml/min, $p < 0.05$), that points to an increase in the arterial vessel conductivity.

NE infusion resulted in an increase in arterial pressure to the maximum of 138 +/- 6 mm Hg at the first 10 min of observation and in simultaneous bradycardia (HR was 153 +/- 8 beats/min). Despite continuation of NE infusion AP began to fall so that at 40 min it did not differ from the initial level. At the same time, the hydraulic resistance in hindquarter vessels rose during 60 min of NE infusion, and at 40 min of infusion the hydraulic resistance was higher than that at 10 min (Table 1). Despite vasoconstriction and increase in hydraulic resistance to the blood flow under NE infusion, the extensibility of arterial vessels increased (Table 1), resulting in a rather small PP increase in response to the rise of volumetric perfusion rate (Fig. 1).

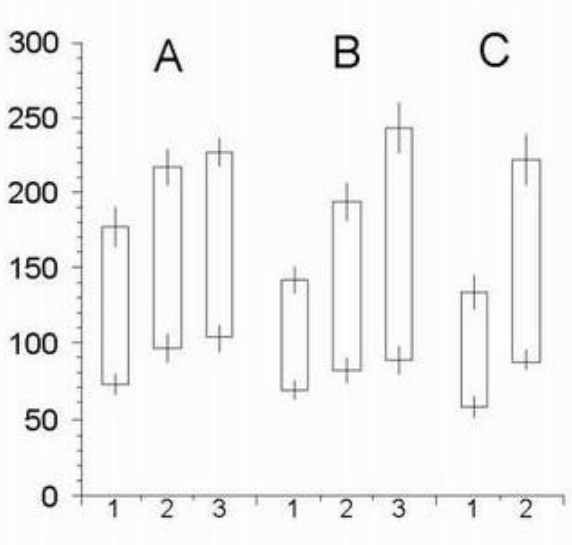

Figure 1. Influence of norepinephrine, NG-nitro-L-arginine and angiotensinamide on the PP gain, caused by increase in the volumetric perfusion rate.
On axis of abscissas - observed groups; on axis of ordinates - size of the PP gain (mm Hg).
On A-1, B-1, C-1 - initial responses; on A-2 - responses on the background of 10 min of NE infusion; on A-3 - responses on the background of 40 min of NE infusion; on B-2 - responses on the background of NG-nitro-L-arginine action; on B-3 - responses after 10 min of NE infusion on the background of NG-nitro-L-arginine action; on C-2 - responses on the background of 15 min of angiotensinamide infusion

Table 1. Influence of norepinephrine, angiotensinamide and NG nitro-L-arginine on parameters of regional haemodynamics with changes of volumetric perfusion rate of hindquarter vascular region.

	Hydraulic resistance of perfused vessels with perfusion by blood volumes (% to initial)		Maximal gain of perfusion pressure with the increase in the perfusion volume (% to initial)	A degree of vessels expansion with the increase in the perfusion volume (% to initial)
	minimal	maximal		
Before NE infusion	100	100	100	100
After 10 min of NE infusion	137 +/- 12 *	126 +/- 9 *	119 +/- 8 *	161 +/- 35 *
After 40 min of NE infusion	149 +/- 10*	132 +/- 8 *	112 +/- 5 *	215 +/- 44*
Before NG nitro-L-arginine injection	100	100	100	100
After NG nitro-L-arginine injection	119 +/- 7 *	135 +/- 5 *	156 +/- 6 *	61 +/- 7 *
Before NE infusion and after NG nitro-L-arginine injection	100	100	100	100
After 20 min of NE infusion	135 +/- 9 *	146 +/- 5 *	157 +/- 2 *	50 +/- 2 *
Before angiotensinamide infusion	100	100	100	100
On the background of 10 min angiotensinamide infusion	150 +/- 9 *	168 +/- 8 *	180 +/- 10 *	70 +/- 7 *

Note: * – $p<0.05$

In the second series, the mean AP was 105 +/- 3 mm Hg, HR was 210 +/- 7 beats/min. The increase in perfusion volumes from 15 +/- 1 to 60 +/- 7 ml/min caused PP increase from 68 +/- 6 to 142 +/- 8 mm Hg and also caused a decrease of resistance to blood flow from 4.8 +/- 0.8 to 2.6 +/- 0.3 mm Hg/ml/min. The AP increased to 135 +/- 5 mm Hg with negligible HR decrease to 191 +/- 8 beats/min after infusion of NG nitro-L-arginine during 15-20 min. The hydraulic resistance in hindquarter vessels increased at all perfusion volumes parallel to a reduction of the vascular extensibility (Table 1). Under this conditions, the PP increase in response to increase in volumetric perfusion rate rose (Fig. 1), and NE infusion caused an additional increase in AP (to 155 +/- 6 mm Hg, $p < 0.05$) without changes in HR. AP maintained at the steady level during 5-7 minutes, and then gradually reduced. At 30 min of NE infusion AP restored to the level that was steady after NO synthesis blockade. The PP increase was observed, and it was higher at the perfusion of vessels by maximal volume of blood and increased during the NE infusion. At 30 min of observation the PP exceeded 250 mm Hg, thereby the dependence «blood flow-pressure» was not determined further. In conditions of NO synthesis blockade NE reduced the vascular extensibility (Table 1) and considerably increased the PP gain that developed in response to increase in volumetric perfusion rate (Fig. 1).

The initial AP in the third series of experiments was 113 +/- 10 mm Hg, HR - 180 +/- 16 beats/min. Increase in perfusion volume from 15 +/- 1 ml/min to 60 +/- 2 ml/min increased PP from 59 +/- 7 to 134 +/- 11 mm Hg ($p < 0.05$) and also reduced resistance to blood flow from 4.6 +/- 0.7 to 2.9 +/- 0.4 mm Hg/ml/min. Angiotensinamide (AN) infusion at 10-15 min of observation increased an AP to 140 +/- 14 mm Hg parallel to a HR relief to 141 +/- 14 beats/min. As it is seen in Table 1 and Figure 1, AN, unlike NE, reduced the vascular extensibility and increased resistance to the blood flow to a the greater degree at maximal perfusion volumes, than at minimal increases the PP gain in response to raises in volumetric perfusion rate.

The observations suggest that NE did not increased but reduced the vascular extensibility in conditions of NO synthesis inhibition. The decrease of the vascular extensibility caused a significant PP gain with the increase in perfusion volume and, thus reduced the ability of vessels to stabilize transmural pressure. We suggest that NO release by NE activity provided an increase in the vascular extensibility in intact animals.

NE is capable of increasing NO release both by direct stimulation of vascular endothelial cells, and by changes in vascular blood flow. Vasoconstrictional activity of the drug can result in increase in the linear blood flow rate and shear stress in endothelium at the perfusion of vascular region by the constant volume of blood [4]. It is known that there is an activation of NO release in these conditions [6]. However, AN, causing vasoconstriction like NE does, reduces the vascular extensibility. Thus, these observations allow us to suggest that the increase in the vascular extensibility by NE was caused by the drug action directly on vascular endotheliocytes.

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