Role of the Renin-Angiotensin System in Regulation of Lung Norepinephrine Inactivation during Hemorrhage

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Previously we demonstrated a decreased lung inactivation of norepinephrine (LIN) at a certain stage of the posthemorrhagic reaction in narcotized rats [3]. We also found that infusion of angiotensin II reduces LIN in a dose-dependent manner [2]. Hemorrhage is known to be accompanied by a substantial activation of the renin-angiotensin system [7], which, in turn, initiates catecholamine release from the adrenal glands [5]. On this basis, we hypothesized that the decreased LIN may be mediated through angiotensin II. To verify this assumption an investigation was undertaken in which LIN was monitored during hemorrhage against the background of captopril, an inhibitor of angiotensin-converting enzyme.

MATERIALS AND METHODS

The experiments were carried out on rats weighing 200-300 g, maintained under standard conditions. The animals were narcotized with nembutal (40 mg/kg, i.p.), the left carotid artery was cannulated, and the right ventricle was catetherized through the right jugular vein. Heparin (500 IU/mg) was injected intravenously into all animals prior to the study. Arterial pressure (AP) in the carotid artery and the right ventricle was monitored with tensometric transducers over the entire experimental period. The first blood sampling for catecholamine determination, which also served as a hemorrhage stimulus, was performed 10 min after intravenous injection of either 1 mg/kg captopril (experimental group, n=10) or the same volume of physiological saline (control group, n=9). Blood was drawn simultaneously from the right ventricle and the carotid artery so that blood loss in each case was 1.5% of the body weight. Twenty-five minutes later, other samples of both arterial and mixed venous blood (1 ml each) were drawn. Additionally, a rheogram for determination of the stroke volume (SV) as described previously [4] and electrocardiogram for determination of the heart rate (HR) were recorded at the following stages: before injections of the drugs, before hemorrhage stimulus, 2 and 15 min after hemorrhage; before the second blood sampling. The data were used for calculation of the minute heart volume (MHV). The content of catecholamines in the blood samples was assessed by HPLC using an electrochemical detector [1]. LIN was calculated according to the formula: $LIN=[(NE_v-NE_a)/NE_v] \times 100\%$. The data were processed using the method of variational statistics.

RESULTS

The obtained results are presented in Fig. 1. Injection of captopril resulted in an AP drop in all rats, the maximum drop being observed 2-5 min postinjection. No marked alterations of blood pressure in the right ventricle or HR were noted. In-

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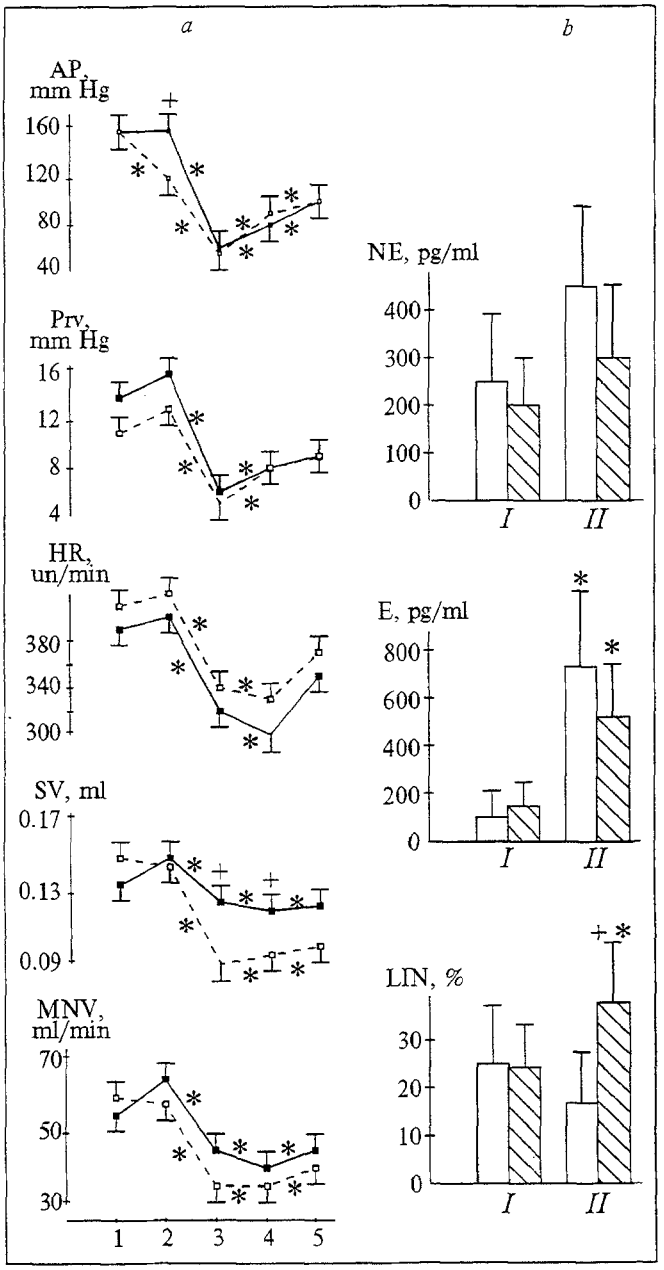

Fig. 1. Dynamics of studied parameters during hemorrhage in control (solid lines, open bars), and captopril – treated rats (broken lines, shaded bars). *a*) Abscissa: *1*) before injection (physiological saline or captopril); *2*) before first blood sampling; *3*, *4*) 2 and 15 min posthemorrhage; *5*) before second blood sampling. *b*) Abscissa: *I*) first blood sampling; *II*) second blood sampling; ordinate: concentrations of norepinephrine (HE) and epinephrine (E) in arterial blood. *: $p<0.05$, intragroup comparison; +: $p<0.05$, intergroup comparison.

jection of physiological saline to control rats produced no reliable changes of AP. The coinciding LIN values in the control and captopril-treated rats suggest the absence of a tonic influence of angiotensin II on LIN. Hemorrhage caused considerable changes in hemodynamics in both groups, the drop of AP and pressure in the right ventricle, SV, and MHV being more pronounced in the experimental group, especially AP after 2 min and SV after 2 and 15 min of hemorrhage ($p<0.05$). Unlike AP, which started to recover as soon as the first few minutes, HR and MHV decreased progressively till 15 min posthemorrhage.

At the 25th min posthemorrhage AP stabilized, although it did not reach the initial level. MHV before the second blood sampling also remained lower than the initial MHV, no differences in MHV between the control and experimental groups being observed. LIN calculated after the second blood sampling was somewhat lower then the initial value in the control, while it surpassed this value 1.5 times in the experimental group ($p<0.05$).

Previously [3] we discovered two stages of LIN dynamics in the acute phase of the posthemorrhagic reaction (up to MHV restoration): 1) an increase with a maximum at the 2nd min; 2) a decrease, starting from the 10th min of hemorrhage. The initial LIN enhancement is evidently related to the MHV decrease and results from a more prolonged contact between the blood and the lung endothelium, whereas the subsequent inhibition of LIN is MHV-independent and thus caused by a different mechanism. In the present study the second blood sampling was performed during the drop of LIN. As expected, LIN in the control animals at this stage was lower than in the first sampling, whereas in the experimental group it was increased at the 25th min posthemorrhage and corresponded to that observed in intact animals during the first few minutes posthemorrhage.

Thus, the inhibition of the renin-angiotensin system with captopril prevented the decrease of LIN, thus suggesting its angiotensin-dependent mechanism. Taking into account the presence of angiotensin II receptors in endothelial cells of the lung vessels [9] and the angiotensin II-mediated inhibition of norepinephrine neuronal uptake [8], which is similar to its lung uptake [6], it may be surmised that the angiotensin-dependent modulation of LIN is due to the direct action of angiotensin II on the lung endotheliocytes.

The data imply one more level of the angiotensin II activating effect on the sympathetic-adrenal system - a metabolic effect: the inhibition of LIN by angiotensin II, which in turn increases the concentration of norepinephrine in the blood. It is significant that this mechanism manifests itself during the substantial activation of the sympathetic-adrenal system which takes place in hemorrhage, when the blood norepinephrine concentration is high enough for its metabolic and vascular effects [10], i.e., its hormonal activity, to kick in.

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Effects of Glutapyrone, a New Amino Acid-Containing 1,4-Dihydropyridine, on Focal Penicillin-Induced Epileptic Activity and on Bicuculline- or Thiosemicarbazide-Induced Convulsions

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Antiepileptic effects of 1,4-dihydropyridines (DHP) have been demonstrated on various animal models of epileptic activity (EpA) and in humans [1] but, being calcium antagonists, these compounds also affect the hemodynamics, which limits their usefulness. Although glutapyrone - a compound synthesized at the Latvian Institute of Organic Synthesis - contains a DHP ring, the sodium salt of glutamic acid attached at position 4 to its molecule makes it a new type of compound (both quantitatively and qualitatively), referred to as an amino acid-containing DHP. Compounds of this type are readily soluble in water, have a low toxicity (LD_{50}>8000 mg/kg intraperitoneally and orally), do not lower arterial pressure [7], and have been shown to exhibit peptide-like regulatory mechanisms of action [8,11]. In addition, glutapyrone has been found to have antiarrhythmic and antiischemic [5,7] as well as antioxidant properties [3].

In this work, we studied glutapyrone for its effects on focal penicillin-induced EpA in the cerebral cortex of rats and on the convulsions induced in mice by bicuculline or thiosemicarbazide.

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MATERIALS AND METHODS

For the study, 211 male Wistar rats weighing 210-260 g and 190 male Icr:Icl mice weighing 19-23 g were used. All animals were maintained in the

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